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Maria V. Rueen

MACROCYCLIC HEPATITIS C SERINE PROTEASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit to US provisional serial nos. _____ (conversion of US 10/365,854), filed February 13, 2003; _____ (conversion of US 10/360,947), filed February 7, 2003; and _____ (conversion of US 10/384,120), filed March 7, 2003, each of which is hereby incorporated by reference in its entirety for any purpose.

TECHNICAL FIELD

The present invention relates to novel macrocycles having activity against hepatitis C virus (HCV) and useful in the treatment of HCV infections. More particularly, the invention relates to macrocyclic compounds, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

HCV is the principal cause of non-A, non-B hepatitis and is an increasingly severe public health problem both in the developed and developing world. It is estimated that the virus infects over 200 million people worldwide, surpassing the number of individuals infected with the human immunodeficiency virus (HIV) by nearly five fold. HCV infected patients, due to the high percentage of individuals inflicted with chronic infections, are at an elevated risk of developing cirrhosis of the liver, subsequent hepatocellular carcinoma and terminal liver disease. HCV is the most prevalent cause of hepatocellular cancer and cause of patients requiring liver transplantations in the western world.

There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

Only two approved therapies for HCV infection are currently available. The original treatment regimen generally involves a 3-12 month course of intravenous interferon-α (IFN-α), while a new approved second-generation treatment involves co-treatment with IFN-α and the general antiviral nucleoside mimics like ribavirin. Both of these treatments suffer from interferon-related side effects as well as low efficacy against HCV infections. There exists a need for the development of effective antiviral agents for treatment of HCV infection due to the poor tolerability and disappointing efficacy of existing therapies.

In a patient population where the majority of individuals are chronically infected and asymptomatic and the prognoses are unknown, an effective drug must possess significantly fewer side effects than the currently available treatments. The hepatitis C non-structural protein-3 (NS3) is a proteolytic enzyme required for processing of the viral polyprotein and consequently viral replication. Despite the huge number of viral variants associated with HCV infection, the active site of the NS3 protease remains highly conserved thus making its inhibition an attractive mode of intervention. Recent success in the treatment of HIV with protease inhibitors supports the concept that the inhibition of NS3 is a key target in the battle against HCV.

HCV is a flaviridae type RNA virus. The HCV genome is enveloped and contains a single strand RNA molecule composed of circa 9600 base pairs. It encodes a polypeptide comprised of approximately 3010 amino acids.

The HCV polyprotein is processed by viral and host peptidase into 10 discreet peptides which serve a variety of functions. There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable

sequence. There are six non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease.

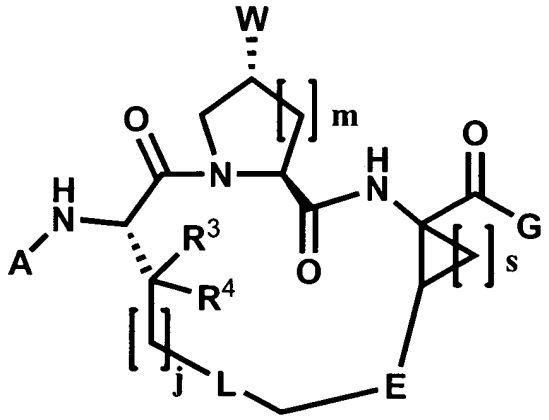
The NS3.4A protease is responsible for cleaving four sites on the viral polyprotein. The NS3-NS4A cleavage is autocatalytic, occurring in cis. The remaining three hydrolyses, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B all occur in trans. NS3 is a serine protease which is structurally classified as a chymotrypsin-like protease. While the NS serine protease possesses proteolytic activity by itself, the HCV protease enzyme is not an efficient enzyme in terms of catalyzing polyprotein cleavage. It has been shown that a central hydrophobic region of the NS4A protein is required for this enhancement. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficacy at all of the sites.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes, including NS3, that are essential for the replication of the virus. Current efforts directed toward the discovery of NS3 protease inhibitors were reviewed by S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current Status and Emerging Strategies, *Nature Rev. Drug Discov.*, **1**, 867-881 (2002). More relevant patent disclosures describing the synthesis of HCV protease inhibitors are: WO 00/59929 (2000); WO 99/07733 (1999); WO 00/09543 (2000); WO 99/50230 (1999); US5861297 (1999).

SUMMARY OF THE INVENTION

The present invention relates to novel macrocyclic compounds and methods of treating a hepatitis C infection in a subject in need of such therapy with said macrocyclic compounds. The present invention further relates to pharmaceutical compositions comprising the compounds of the present invention, or pharmaceutically acceptable salts, esters, or prodrugs thereof, in combination with a pharmaceutically acceptable carrier or excipient.

A compound having the Formula I or a pharmaceutically acceptable salt, ester or prodrug thereof:



I

wherein:

A is selected from the group consisting of H, - (C=O)-R^2, -(C=O)-O-R^1 , -C(=O)-NH-R^2, -C(=S)-NH-R^2, –$S(O)_2$-R^2, -(C=NR^1)-R^1, and -(C=NR^1)-NH-R^1;

G is selected from the group consisting of -OH, -O-(C_1-C_{12} alkyl), -NH$S(O)_2$ -R^1, -(C=O)-R^1, -(C=O)-R^2, -(C=O)-O-R^1, –(C=O)-NH-R^1, and –(C=O)-NH-R^2 ;

L is selected from the group consisting of absent, -S-, -SCH_2-, -SCH_2CH_2-, -$S(O)_2$-, -$S(O)_2CH_2CH_2$-, -S(O)-, -S(O)CH_2CH_2-, -O-, -OCH_2-, -OCH_2CH_2-, -(C=O)-CH_2-, -$CH(CH_3)CH_2$-, -$CFHCH_2$-, –CF_2CH_2-, and –CR_x=CR_x- where R_x = H or halogen;

j is 0, 1, 2, 3, or 4;

m is 0, 1, or 2;

s is 0, 1 or 2;

R^1 is selected form the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

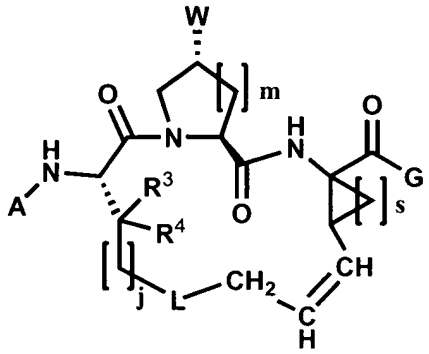
R^2 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, alkylamino, dialkylamino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, OH, CH_3, CN, SH, halogen, NO_2, NH_2, amide, methoxy, trifluoromethoxy, and trifluoromethyl;

E represents either a single bond or a double bond between the two carbon atoms attached thereto; and

W is a substituted or unsubstituted heterocyclic ring system.

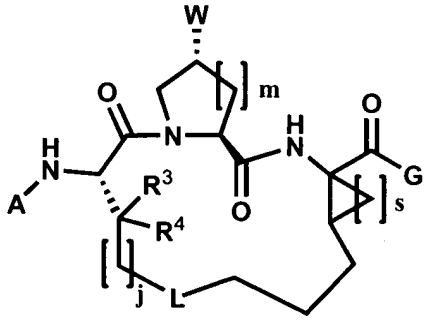
In one embodiment of the present invention E represents a double bond, resulting in Formula II or pharmaceutically acceptable salts, esters, or prodrugs thereof:



(II)

wherein the remaining substitutents are as described above.

In one embodiment of the present invention E represents a single bond, resulting in Formula III or pharmaceutically acceptable salts, esters, or prodrugs thereof:

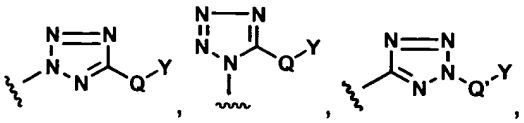
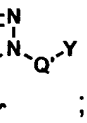


(III)

wherein the remaining substituents are as described above.

In one embodiment of the present invention there are disclosed compounds represented by Formulas II and III, or pharmaceutically acceptable salts, esters, or prodrugs thereof:

wherein

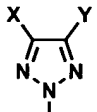
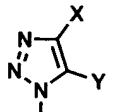
W is selected from the group consisting of:  , 
and  ;

Q is selected from the group consisting of: absent, $-CH_2-$, $-O-$, $-NH-$, $-N(R^1)-$, $-S-$, $-S(O)_2-$, and $-(C=O)-$;

Q' is selected from the group consisting of: absent, $-CH_2-$, and $-NH-$; Y is selected from the group consisting of: H, C_1-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

All other substituents are as defined above.

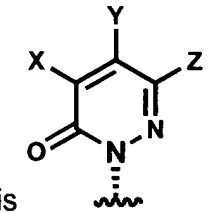
In one embodiment of the present invention there are disclosed compounds represented by Formulas II and III, or pharmaceutically acceptable salts, esters, or prodrugs thereof wherein

W is selected from the group consisting of:  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $-CH_2$-alkylamino, $-CH_2$-dialkylamino, $-CH_2$-arylamino, $-CH_2$-diarylamino, $-(C=O)$-alkylamino, $-(C=O)$-dialkylamino, $-(C=O)$-arylamino, $-(C=O)$-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form

a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

All other substituents are as defined above.

In one embodiment of the present invention there are disclosed compounds represented by Formulas II and III, or pharmaceutically acceptable salts, esters, or prodrugs thereof wherein:



W is and

X, Y, and Z are independently selected from the group consisting of H, N_3, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, alkylamino, dialkylamino, C_1–C_6 alkynyl, substituted alkynyl, aryl, substituted aryl, –S–aryl, –S–substituted aryl, –O–aryl, –O–substituted aryl, NH–aryl, NH–substituted aryl, diarylamino, diheteroarylamino, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, –S–heteroaryl, –S–substituted heteroaryl, –O–heteroaryl, –O–substituted heteroaryl, –NH–heteroaryl, –NH–substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; or, in the alternative, X and Y or Y and Z taken together with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl, or substituted heteroaryl cyclic moiety.

Other aspects of the invention are:

A compound according to any of the formulae herein wherein W is substituted with one or more substituents, each of said substituents being independently selected from any of (a), (b), (c), (d) and (e):

(a) alkenyl; alkoxy; alkoxyalkyl; alkyl; alkylamino; alkylaryl; alkylsulfonyl; alkynyl; amide; amido optionally mono-substituted with C_1-C_6 alkyl; aryl; arylalkanoylalkyl; arylalkyl; arylaminoalkyl; aryloxyalkyl; arylsulfonyl; cycloalkoxy; cycloalkyl; dialkylamino; dialkylaminoalkyl; diarylaminoalkyl; haloalkyl; heteroaryl; heteroarylalkyl; heterocyclo;

heterocycloalkyl; heterocycloalkylalkyl; thioalkyl; monoalkylaminoalkyl; sulfonyl; (lower alkyl)sulfonyl; haloalkyl; carboxyl; amide; (lower alkyl)amide; heterocyclo optionally substituted with C_1-C_6 alkyl; perhaloalkyl; sulfonyl; thioalkyl; urea, $C(=O)-R^{11}$; $OC(=O)R^{11}$; $C(=O)O-R^{11}$; $C(=O)N(R^{11})_2$; $C(=S)N(R^{11})_2$; SO_2R^{11}; $NHS(O_2)R^{11}$; $N(R^{12})_2$; $N(R^{12})C(=O)R^{11}$;

wherein each of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy, perhaloalkyl;

(b) C_7-C_{14} aralkyl; C_2-C_7cycloalkyl; C_6-C_{10} aryl; heterocyclo; (lower alkyl)-heterocyclo;

wherein each aralkyl, cycloalkyl, aryl, heterocyclo or (lower alkyl)-heterocyclo may be optionally substituted with R^6, where R^6 is halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy, NO_2, $N(R^7)_2$, NH-C(O)-R^7 or NH-C(O)-NHR^7; where R^7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

or R^6 is NH-C(O)-OR^8 where R^8 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

(c) $N(R^5)_2$, NH-C(O)-R^5, or NH-C(O)-NH-R^5 where R^5 is independently H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, C_6 or C_{10} aryl, C_7-C_{14} aralkyl, heterocyclo or (lower alkyl)-heterocyclo;

(d) NH-C(O)-OR^8 where R^8 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

(e) formyl; halogen;, hydroxy; NO_2; OH; SH; halo; CN;

wherein

each R^{11} is independently H, OH, alkyl, alkenyl, alkynyl, perhaloalkyl, alkoxy, aryl, arylalkyl, alkylaryl, heterocyclo, heterocycloalkyl, alkylsulfonyl, arylsulfonyl, heteroaryl, heteroarylalkyl, arylalkanoylalkyl, heterocycloalkylalkyl aryloxyalkyl, alkylamino, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, wherein any of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy and perhaloalkyl; and

each R^{12} is independently H, formyl, alkyl, alkenyl, alkynyl, perhaloalkyl, alkoxy, aryl, arylalkyl, alkylaryl, heterocyclo, heterocycloalkyl, alkylsulfonyl, arylsulfonyl, heteroarylalkyl, heteroaryl, arylalkanoylalkyl, heterocycloalkylalkyl aryloxyalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, or

diarylaminoalkyl, wherein any of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy and perhaloalkyl;

The compound of any of the formulae herein wherein W is selected from the group consisting of:

(a) an aliphatic heteromonocyclic, heterobicyclic or heterotricyclic ring system having from five to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl, R^{10} and R^{11}; and

(b) an aromatic heteromonocyclic, heterobicyclic or heterotricyclic ring system having from five to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl, and R^{10};

wherein:

each R^{10} is independently alkyl, alkenyl, alkynyl, perhaloalkyl, alkoxy, aryl, arylalkyl, alkylaryl, heterocyclo, heterocycloalkyl, alkylsulfonyl, arylsulfonyl, heretoaryl, heteroarylalkyl, arylalkanoylalkyl, heterocycloalkylalkyl aryloxyalkyl, alkylamino, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, heteroaryl or urea, wherein any of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy and perhaloalkyl; $C(=O)$-R^{11}, $OC(=O)R^{11}$, $C(=O)O$-R^{11}, $C(=O)N(R^{11})_2$, $C(=S)N(R^{11})_2$, SO_2R^{11}, $NHS(O_2)R^{11}$, $N(R^{12})_2$, and $N(R^{12})C(=O)R^{11}$;

each R^{11} is independently H, OH, alkyl, alkenyl, alkynyl, perhaloalkyl, alkoxy, aryl, arylalkyl, alkylaryl, heterocyclo, heterocycloalkyl, alkylsulfonyl, arylsulfonyl, heteroaryl, heteroarylalkyl, arylalkanoylalkyl, heterocycloalkylalkyl aryloxyalkyl, alkylamino, dialkylamino, monoalkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, wherein any of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy and perhaloalkyl;

each R^{12} is independently H, formyl, alkyl, alkenyl, alkynyl, perhaloalkyl, alkoxy, aryl, arylalkyl, alkylaryl, heterocyclo, heterocycloalkyl, alkylsulfonyl, arylsulfonyl,

heteroarylalkyl, heteroaryl, arylalkanoylalkyl, heterocycloalkylalkyl aryloxyalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, or diarylaminoalkyl, wherein any of the foregoing can be optionally be substituted with up to three groups selected from halogen, OH, alkoxy and perhaloalkyl;

The compound of any of the formulae herein wherein W is an aliphatic heteromonocyclic, heterobicyclic or heterotricyclic ring system having from five to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl, R_{10} and R_{11};

The compound of any of the formulae herein wherein W is an aliphatic heteromonocyclic ring system having from five to seven ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl, R^{10} and R^{11};

The compound of any of the formulae wherein said optionally substituted aliphatic heteromonocyclic ring system has five ring atoms and 1 or 2 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heteromonocyclic ring system is selected from the group consisting of pyrrolidines, pyrazolidines, pyrrolines, tetrahydrothiophenes, dihydrothiophenes, tetrahydrofurans, dihydrofurans, imidazolines, tetrahydroimidazoles, dihydropyrazoles, tetrahydropyrazoles, and oxazolines;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heteromonocyclic ring system has six ring atoms and 1 or 2 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heteromonocyclic ring system is selected from the group consisting of pyridines, piperidines, dihydropyridines, tetrahydropyridines, dihydropyrans, tetrahydropyrans, dioxanes, piperazines, dihydropyrimidines, tetrahydropyrimidines, perhydro pyrimidine, morpholine, thioxane, and thiomorpholine;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heteromonocyclic ring system has seven ring atoms and 1 or 2 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heteromonocyclic ring system is selected from the group consisting of hexamethyleneimine, and hexamethylenesulfide;

The compound of any of the formulae herein wherein W is an aliphatic heterobicyclic ring system having from five to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl and R_{10}.

The compound of any of the formulae herein wherein said optionally substituted aliphatic heterobicyclic ring system has eight to twelve ring atoms and 1 to 4 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aliphatic heterobicyclic ring system eight to twelve ring atoms and 1 or 2 ring hetero atoms selected from O and N;

The compound of any of the formulae herein wherein W is an aromatic heteromonocyclic, heterobicyclic or heterotricyclic ring system having from five to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein

said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl and R_{10};

The compound of any of the formulae herein wherein W is an aromatic heteromonocyclic ring system having from five to seven ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl and R_{10};

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system has five ring atoms and 1 or 2 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system is selected from the group consisting of pyrroles, pyrazoles, porphyrins, furans, thiophenes, pyrazoles, imidazoles, oxazoles, oxadiazoles, isoxazoles, thiazoles, thiadiazoles, and isothiazoles;

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system has six ring atoms and 1, 2 or 3 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system is selected from the group consisting of pyridines, pyrimidines, pyrazines, pyrans, and triazines;

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system has five ring atoms and 3 or 4 ring hetero atoms selected from O, N and S;

The compound of any of the formulae herein wherein said optionally substituted aromatic heteromonocyclic ring system is triazolyl or tetrazolyl;

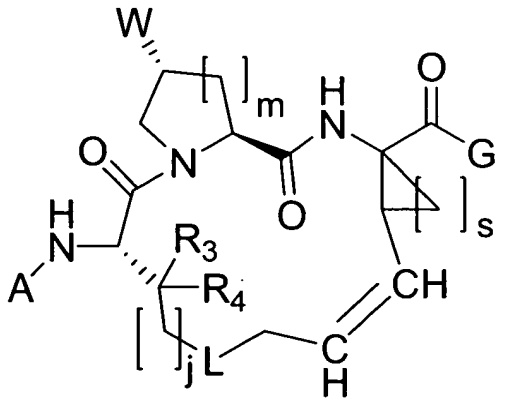
The compound of any of the formulae herein wherein W is an aromatic heterobicyclic ring system having from eight to twelve ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl and R_{10};

The compound of any of the formulae herein wherein said optionally substituted aromatic heterobicyclic ring system is selected from the group consisting of adenines, azabenzimidazoles, azaindoles, benzimidazoles, benzo isothiazoles, benzofurans, benzoisoxazoles, benzooxazoles, benzothiadiazoles, benzothiazoles, benzothienes, benzothiophenes, benzoxazoles, carbazoles, cinnolines, guanines, imidazopyridines, indazoles, indoles, isoindoles, isoquinolines, phthalazines, purines, pyrrolo pyridines, quinazolines, quinolines, quinoxalines, thianaphthenes, and xanthines;

The compound of any of the formulae herein wherein W is an aromatic heterotricyclic ring system having from ten to sixteen ring atoms and up to four ring hetero atoms selected from O, N and S, wherein said ring system is optionally substituted with up to three ring substituents selected from the group consisting of OH, CN, halogen, formyl, R_{10} and R_{11}; and

The compound of any of the formulae herein wherein said optionally substituted aromatic heterotricyclic ring system is selected from the group consisting of carbazoles, bibenzofurans, psoralens, dibenzothiophenes, phenazines, thianthrenes, phenanthrolines, phenanthridines.

Other embodiments are a compound of Formula II



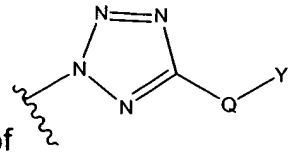
Formula II

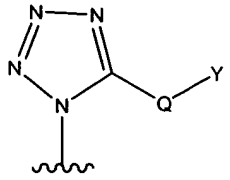
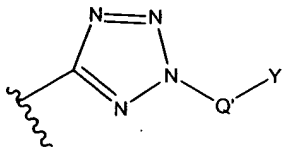
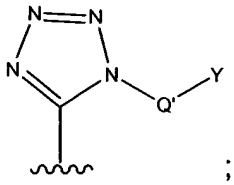
Wherein:

A is selected from the group consisting of H, -(C=O)-R^2, -(C=O)-O-R^l, -C(=O)-NH-R^1, -C(=S)-NH-R^2 , –$S(O)_2$-R^2, -(C=NR^1)-R^1, and -(C=NR^1)-NH-R^1;

G is selected from the group consisting of -OH, -O-(C_1-C_{12} alkyl), -$NHS(O)_2$-R^l, -(C=O)-R^2, -(C=O)-O-R^l, and -(C=O)-NH-R^2;

L is selected from the group consisting of absent, -S-, -SCH_2-, -SCH_2CH_2-, -$S(O)_2$-, -$S(O)_2CH_2CH_2$-, -S(O)-, -$S(O)CH_2CH_2$-, -O-, -OCH_2-, -OCH_2CH_2-, -(C=O)-CH_2-, -$CH(CH_3)CH_2$-, -$CFHCH_2$-, –CF_2CH_2-, and –CR_x=CR_x- where R_x = H or halogen;

W is selected from the group consisting of  ,

 ,  , and  ;

Q is selected from the group consisting of absent, -CH_2-, -O-, -NH-, -N(R^1)-, -S-, -$S(O)_2$-, and -(C=O)-;

Q' is selected from the group consisting of absent, -CH_2-, and -NH-;

Y is selected from the group consisting of H, C_l-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0,1 or 2;

R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

R^2 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and

R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

A compound of theabove formula II, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound of theabove formula II, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

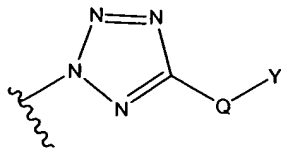
R^3 and R^4 are hydrogen;

A compound of theabove formula II, wherein:

A is -(C=O)-O-R^1,

G is hydroxyl;

L is absent;

W is 

j = 3;

m = s = 1; and

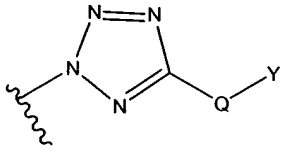
R^3 and R^4 are hydrogen; and

A compound of theabove formula II, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

W is 

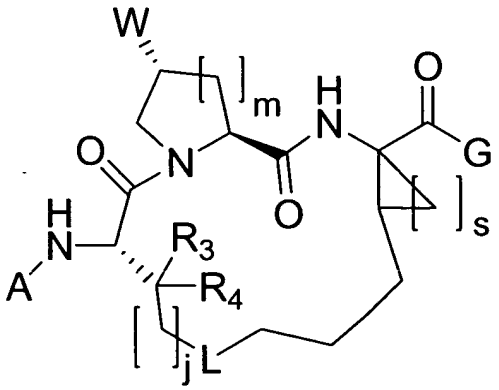
j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen.

Other embodiments are:

A compound of Formula III:



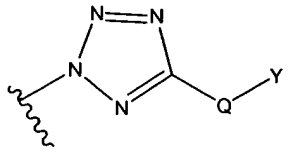
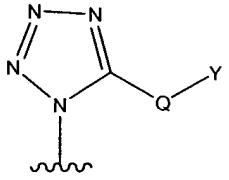
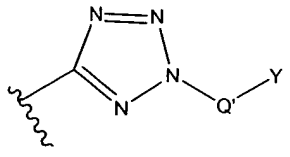
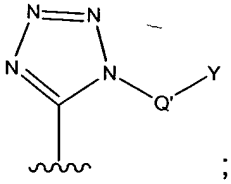
Formula III

wherein

A is selected from the group consisting of H, -(C=O)-R^2, -(C=O)-O-R^1, -C(=O)-NH-R^2, -C(=S)-NH-R^2 , $-S(O)_2-R^2$, -(C=NR^1)-R^1, and -(C=NR^1)-NH-R^1;

G is selected from the group consisting of -OH, -O-(C_1-C_{12} alkyl), -$NHS(O)_2$-R^1, -(C=O)-R^2, -(C=O)-O-R^1, and -(C=O)-NH-R^2;

L is selected from the group consisting of absent, -S-, $-SCH_2-$, $-SCH_2CH_2-$, $-S(O)_2-$, $-S(O)_2CH_2CH_2-$, -S(O)-, $-S(O)CH_2CH_2-$, -O-, $-OCH_2-$, $-OCH_2CH_2-$, -(C=O)-CH_2-, $-CH(CH_3)CH_2-$, $-CFHCH_2-$, $-CF_2CH_2-$, and $-CR_x=CR_x-$ where R_x = H or halogen;

W is selected from the group consisting of  ,  ,  , and  ;

Q is selected from the group consisting of absent, $-CH_2-$, -O-, -NH-, -N(R^1)-, -S-, $-S(O)_2-$, and -(C=O)-;

Q' is selected from the group consisting of absent, $-CH_2-$, and -NH-;

Y is selected from the group consisting of H, C_1-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0,1 or 2;

R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

R^2 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino,

diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and

R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

A compound according to formula III above, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

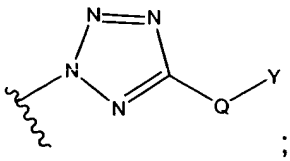
R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

W is  ;

j = 3;

m = s = 1; and

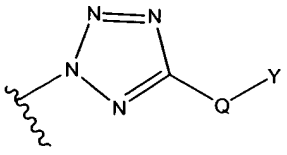
R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

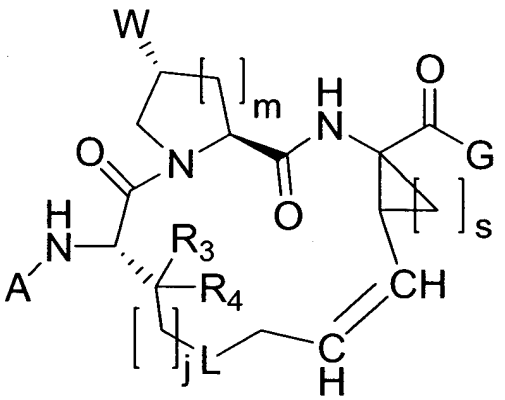
W is 

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound of Formula II:



Formula II

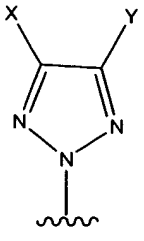
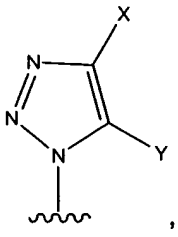
wherein

A is selected from the group consisting of H, -(C=O)-R^2, -(C=O)-O-R^l, -C(=O)-NH-R^2, -C(=S)-NH-R^2 , –$S(O)_2$-R^2, -(C=NR^1)-R^1, and -(C=NR^1)-NH-R^1;

G is selected from the group consisting of -OH, -O-(C_1-C_{12} alkyl), -NHS$(O)_2$-R^l, -(C=O)-R^2, -(C=O)-O-R^l, and -(C=O)-NH-R^2;

L is selected from the group consisting of absent, -S-, -SCH_2-, -SCH_2CH_2-,

$-S(O)_2-$, $-S(O)_2CH_2CH_2-$, $-S(O)-$, $-S(O)CH_2CH_2-$, $-O-$, $-OCH_2-$, $-OCH_2CH_2-$, $-(C=O)-CH_2-$, $-CH(CH_3)CH_2-$, $-CFHCH_2-$, $-CF_2CH_2-$, and $-CR_x=CR_x-$ where R_x = H or halogen;

W is selected from the group consisting of  and  ,

where X and Y are independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $-CH_2$-alkylamino, $-CH_2$-dialkylamino, $-CH_2$-arylamino, $-CH_2$-diarylamino, -(C=O)-alkylamino, -(C=O)-dialkylamino, -(C=O)-arylamino, -(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, for a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0, 1 or 2;

R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

R^2 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and

R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

A compound according to formula II above, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

j = 3;

m=s=1; and

R^3 and R^4 are hydrogen;

A compound according to formula II above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

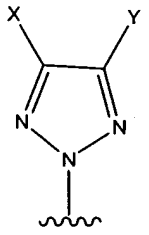
R^3 and R^4 are hydrogen;

A compound according to formula II above, wherein:

A is -(C=O)-O-R^1,

G is hydroxyl;

L is absent;



W is

j = 3;

m = s = 1; and

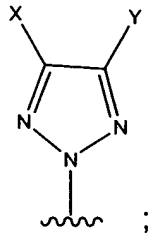
R^3 and R^4 are hydrogen;

A compound according to formula II above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;



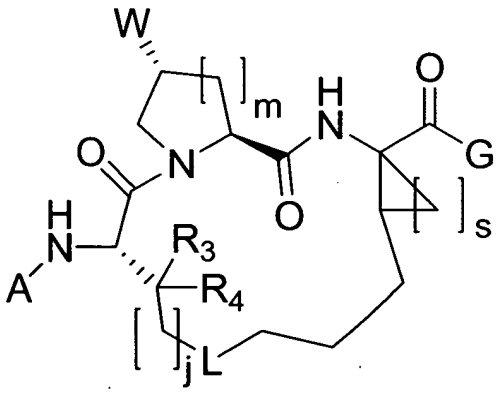
W is ;

J = 3;

M = s = 1; and

R^3 and R^4 are hydrogen.

Other embodiments are a compound of Formula III:



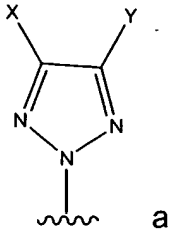
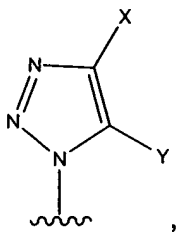
Formula III

wherein

A is selected from the group consisting of H, -(C=O)-R^2, -(C=O)-O-R^1, -C(=O)-NH-R^2, -C(=S)-NH-R^2 , –$S(O)_2$-R^2, -(C=NR^1)-R^1, and -(C=NR^1)-NH-R^1;

G is selected from the group consisting of -OH, -O-(C_1-C_{12} alkyl), -$NHS(O)_2$-R^l, -(C=O)-R^2, -(C=O)-O-R^l, and -(C=O)-NH-R^2;

L is selected from the group consisting of absent, -S-, -SCH_2-, -SCH_2CH_2-, -$S(O)_2$-, -$S(O)_2CH_2CH_2$-, -O-, -OCH_2-, -OCH_2CH_2-, -(C=O)-CH_2-, -$CH(CH_3)CH_2$-, -$CFHCH_2$- , –CF_2CH_2-, and –CR_x=CR_x- where R_x = H or halogen;

from the group consisting of  and  , where X and Y are independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, -CH_2-alkylamino, -CH_2-dialkylamino, -CH_2-arylamino, -CH_2-diarylamino, -(C=O)-alkylamino, -(C=O)-dialkylamino, -(C=O)-arylamino, -(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, for a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0, 1 or 2;

R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl;

R^2 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and

R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

A compound according to formula III above, wherein:

A is -(C=O)-O-R^l;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

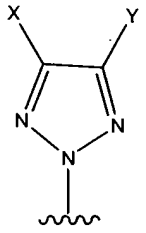
R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-R^l,

G is hydroxyl;

L is absent;



W is

j = 3;

m = s = l; and

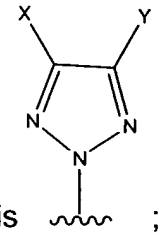
R^3 and R^4 are hydrogen;

A compound according to formula III above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;



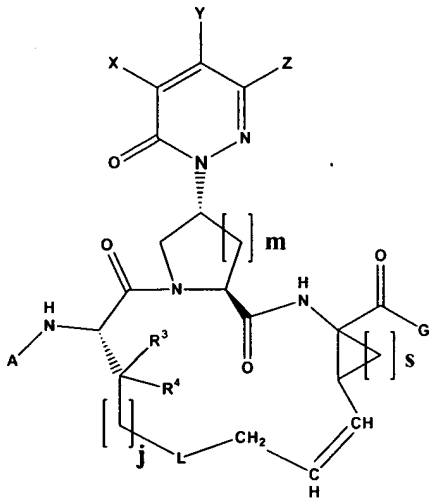
W is ~~~ ;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound of Formula IV:



(IV)

wherein

A is hydrogen, -(C=O)-R^1 , -(C=O)-O-R^1, -C(=O)-NH-R^2 , -C(=S)-NH-R^2, –$S(O)_2$-R^2, -(C=NR^1)-R^1, or -(C=NR^1)-NH-R^1;

G is -OH, -O-(C_1-C_{12} alkyl), -$NHS(O)_2$-R^l, -(C=O)-R^2, -(C=O)-O-R^l, or -(C=O)-NH-R^2;

L is -S-, -SCH_2-, -SCH_2CH_2-, -$S(O)^2$-, -$S(O)^2CH^2CH^2$-, -S(O)-, -$S(O)CH_2CH_2$-, -O-, -OCH_2-, -OCH_2CH_2-, -(C=O)-CH_2-, -$CH(CH_3)CH_2$-, -$CFHCH_2$- –CF_2CH_2-, or –CR_x=CR_x- where R_x = H or halogen;

X, Y, and Z are independently selected from the group consisting of hydrogen, N_3, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, alkylamino, dialkylamino, C_1-C_6 alkynyl, substituted alkynyl, aryl, substituted aryl, -S-aryl, -S-substituted aryl, -O-aryl, -O-substituted aryl, NH-aryl, NH-substituted aryl, diarylamino, diheteroarylamino, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, -S-heteroaryl, -S-substituted heteroaryl, -O-heteroaryl, -O-substituted heteroaryl, -NH-heteroaryl, -NH-substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; or,

in the alternative, X and Y or Y and Z taken together with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl, or substituted heteroaryl cyclic moiety;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0, 1 or 2;

R^1 is hydrogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl; and

R^3 and R^4 are each independently hydrogen or methyl;

A compound according to formula IV above, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound according to formula IV above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

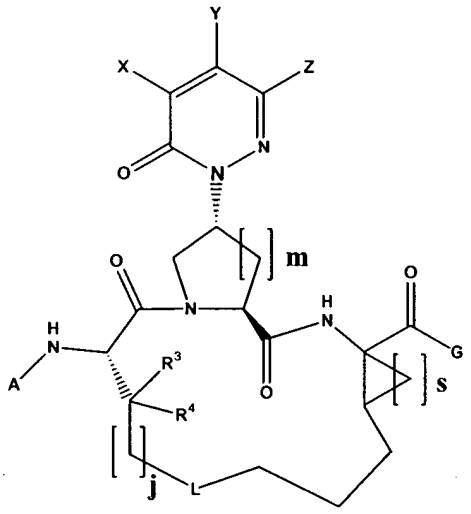
L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen;

A compound of Formula V:



(V)

wherein

A is hydrogen, -(C=O)-R^1 , -(C=O)-O-R^l, -C(=O)-NH-R^2 , -C(=S)-NH-R^2 , or –$S(O)_2$-R^2, -(C=NR^1)-R^1, or -(C=NR^1)-NH-R^1;

G is -OH, -O-(C_1-C_{12} alkyl), -NHS$(O)_2$-R^i, -(C=O)-R^2, -(C=O)-O-R^l, or -(C=O)-NH-R^2;

L is absent, -S-, -SCH_2-, -SCH_2CH_2-, -$S(O)_2$-, -$S(O)_2CH_2CH_2$-, -S(O)-, -$S(O)CH_2CH_2$-, -O-, -OCH_2-, -OCH_2CH_2-, -(C=O)-CH_2-, -$CH(CH_3)CH_2$-, -$CFHCH_2$-, –CF_2CH_2-, or –CR_x=CR_x- where R_x = H or halogen -;

X, Y, and Z are independently selected from the group consisting of hydrogen, N_3, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, alkylamino, dialkylamino, C_1-C_6 alkynyl, substituted alkynyl, aryl, substituted aryl, -S-aryl, -S-substituted aryl, -O-aryl, -O-substituted aryl, NH-aryl, NH-substituted aryl, diarylamino, diheteroarylamino, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, -S-heteroaryl, -S-substituted heteroaryl,

-O-heteroaryl, -O-substituted heteroaryl, -NH-heteroaryl, -NH-substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; or,

in the alternative, X and Y or Y and Z taken together with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl, and substituted heteroaryl cyclic moiety;

j = 0, 1, 2, 3, or 4;

m = 0, 1, or 2;

s = 0, 1 or 2;

R^1 is hydrogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R^2 is hydrogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl; and

R^3 and R^4 are each independently hydrogen or methyl;

A compound according to formula V above, wherein:

A is -(C=O)-O-R^1;

G is hydroxyl;

L is absent;

j = 3;

m = s = 1; and

R^3 and R^4 are hydrogen; and

A compound according to formula V above, wherein:

A is -(C=O)-O-*tert*-butyl;

G is hydroxyl;

L is absent;

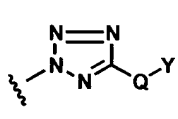
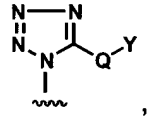
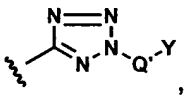
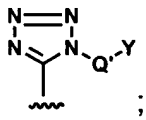
j = 3;

m = s = 1; and

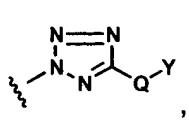
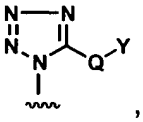
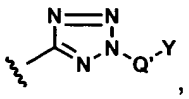
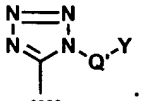
R^3 and R^4 are hydrogen.

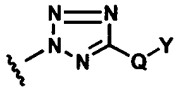
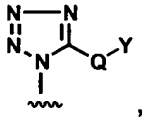
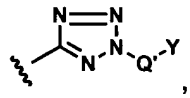
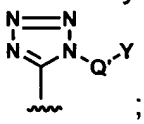
Other embodiments are:

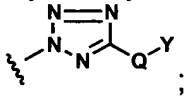
compounds of formulae II or III as delineated herein, wherein:

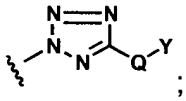
A is selected from the group consisting of: H, –(C=O)–R^2, –(C=O)–O–R^1, –C(=O)–NH–R^2, –C(=S)–NH–R^2, and –$S(O)_2$–R^2; G is selected from the group consisting of: –OH, –O–(C_1–C_{12} alkyl), –$NHS(O)_2$–R^1, –(C=O)–R^1, –(C=O)–O–R^1, and –(C=O)–NH–R^1; L is selected from the group consisting of: absent, –S–, –SCH_2–, –SCH_2CH_2–, –$S(O)_2$–, –$S(O)_2CH_2CH_2$–, –S(O)–, –$S(O)CH_2CH_2$–, –O–, –OCH_2–, –OCH_2CH_2–, –(C=O)–CH_2–, –$CH(CH_3)CH_2$–, –$CFHCH_2$–, and –CF_2CH_2–; W is selected from the group consisting of:  ,  ,  , and  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –$S(O)_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j = 0, 1, 2, 3, or 4; m = 0, 1, or 2; s = 0, 1 or 2; R^1 is selected from the group consisting of: H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl,

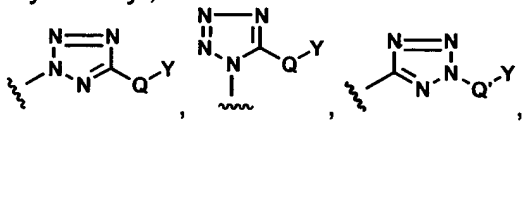
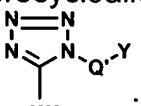
arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; R^2 is selected from the group consisting of: H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

compounds of formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ,  ,  ,  and  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –$S(O)_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

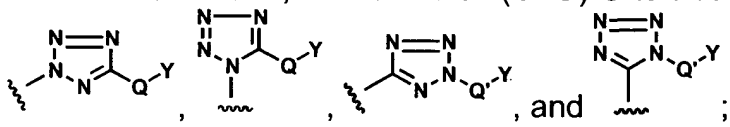
Compounds of formula II wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ,  ,  , and  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –$S(O)_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

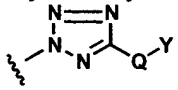
Compounds of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

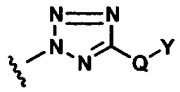
Compounds of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  and  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,

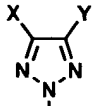
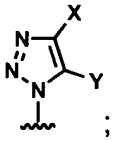
heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, $-O-$, $-NH-$, $-N(R^1)-$, $-S-$, $-S(O)_2-$, and $-(C=O)-$; Q' is selected from the group consisting of: absent, $-CH_2-$, and $-NH-$; Y is selected from the group consisting of: H, C_1-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

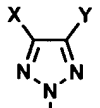
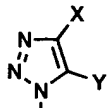
Compounds of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, $-O-$, $-NH-$, $-N(R^1)-$, $-S-$, $-S(O)_2-$, and $-(C=O)-$; Y is selected from the group consisting of: H, C_1-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen; and

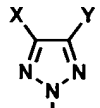
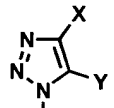
Compounds of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, $-O-$, $-NH-$, $-N(R^1)-$, $-S-$, $-S(O)_2-$, and $-(C=O)-$; Y is selected from the group consisting of: H, C_1-C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen.

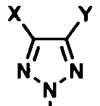
Other embodiments are:

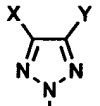
Compounds of formulae II or III wherein wherein A is selected from the group consisting of: H, $-(C=O)-R^2$, $-(C=O)-O-R^1$, $-C(=O)-NH-R^2$, $-C(=S)-NH-R^2$, and $-S(O)_2-R^2$; G is selected from the group consisting of: –OH, $-O-(C_1-C_{12}$ alkyl), $-NHS(O)_2-R^1$, $-(C=O)-R^2$, $-(C=O)-O-R^1$, and $-(C=O)-NH-R^2$; L is selected from the group consisting of: absent, –S–, $-SCH_2-$, $-SCH_2CH_2-$, $-S(O)_2-$, $-S(O)_2CH_2CH_2-$, –S(O)–, $-S(O)CH_2CH_2-$, –O–, $-OCH_2-$, $-OCH_2CH_2-$, $-(C=O)-CH_2-$, $-CH(CH_3)CH_2-$, $-CFHCH_2-$ and $-CF_2CH_2-$; W is selected from the group consisting of:  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, $-CH_2$-alkylamino, $-CH_2$-dialkylamino, $-CH_2$-arylamino, $-CH_2$-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j = 0, 1, 2, 3, or 4; m = 0, 1, or 2; s = 0, 1, or 2; R^1 is selected from the group consisting of: H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; R^2 is selected from the group consisting of: H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and methyl;

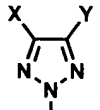
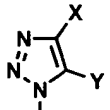
A compound of Formula II, wherein A is $-(C=O)-O-R^1$, R^1 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl,

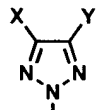
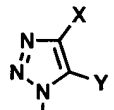
substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is selected from the group consisting of:,  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

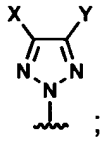
A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is selected from the group consisting of:  or  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

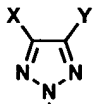
A compound of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

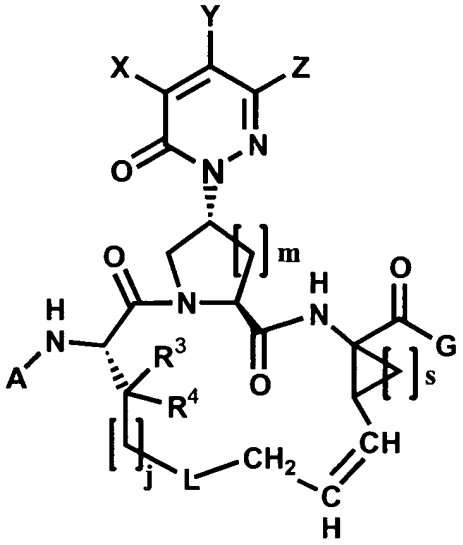
A compound of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is selected from the group consisting of:,  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is selected from the group consisting of:  or  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

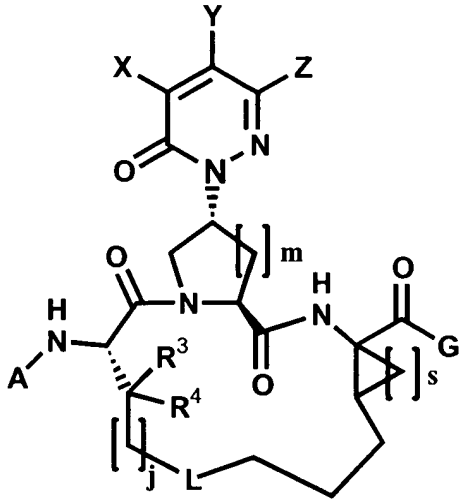
A compound of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen; and

A compound of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen.

Other embodiments are compounds of formulae IV or V:



(IV)



(V)

wherein A is H, $-(C=O)-R^2$, $-(C=O)-O-R^1$, $-C(=O)-NH-R^2$, $-C(=S)-NH-R^2$, or $-S(O)_2-R^2$; G is –OH, $-O-(C_1-C_{12}$ alkyl), $-NHS(O)_2-R^1$, $-(C=O)-R^2$, $-(C=O)-O-R^1$, or $-(C=O)-NH-R^2$; L is absent, –S–, $-SCH_2-$, $-SCH_2CH_2-$, $-S(O)_2-$, $-S(O)_2CH_2CH_2-$, –S(O)–, $-S(O)CH_2CH_2-$, –O–, $-OCH_2-$, $-OCH_2CH_2-$, $-(C=O)-CH_2-$, $-CH(CH_3)CH_2-$, $-CFHCH_2-$ or $-CF_2CH_2-$; X, Y, and Z are independently selected from the group consisting of H, N_3, halogen, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, alkylamino, dialkylamino, C_1-C_6 alkynyl, substituted alkynyl, aryl, substituted aryl, –S–aryl, –S–substituted aryl, –O–aryl, –O–substituted aryl, NH–aryl, NH–substituted aryl, diarylamino, diheteroarylamino, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, –S–heteroaryl, –S–substituted heteroaryl, –O–heteroaryl, –O–substituted heteroaryl, –NH–heteroaryl, –NH–substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; or, in the alternative, X and Y or Y and Z taken together with the carbon atoms to which they are attached form an aryl, substituted aryl, heteroaryl, or substituted heteroaryl cyclic moiety; j = 0, 1, 2, 3, or 4; m = 0, 1, or 2; s = 0, 1, or 2; R^1 is H, C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl,

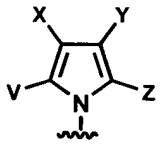
heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl; R^2 is H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, alkylamino, dialkyl amino, arylamino, diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, or substituted heterocycloalkyl; and R^3 and R^4 are each independently hydrogen or methyl;

A compound of Formula IV, wherein A is -(C=O)-O-R^1 ; G is hydroxyl; L is absent; ; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula IV, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula V, wherein A is -(C=O)-O-R^1; L is absent; j=3; m=s=1; and R^3 and R^4 are hydrogen; and

A compound of Formula V, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; j=3; m=s=1; and R^3 and R^4 are hydrogen.

Another aspect is a compound of formula I, wherein W is 

wherein V, X, Y, and Z are each independently selected from:

a) –C_1–C_6 alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

b) –C_2–C_6 alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from

halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

c) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

d) aryl;

e) substituted aryl;

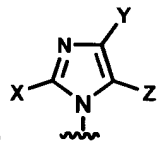
f) heteroaryl;

g) substituted heteroaryl;

h) heterocycloalkyl; or

i) substituted heterocycloalkyl;

or in the alternative, V and X, X and Y, or Y and Z are taken together with the carbons to which they are attached to for a cyclic moiety selected from: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

Another aspect is a compound of formula I, wherein W is 

wherein X, Y, and Z are each independently selected from:

a) $-C_1-C_6$ alkyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

b) $-C_2-C_6$ alkenyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

c) $-C_2-C_6$ alkynyl containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N, optionally substituted with one or more substituent selected from

halogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

d) aryl;

e) substituted aryl;

f) heteroaryl;

g) substituted heteroaryl;

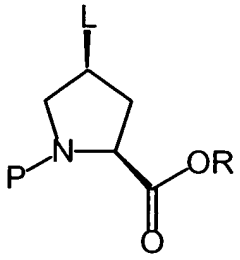
h) heterocycloalkyl; or

i) substituted heterocycloalkyl;

or in the alternative, Y and Z are taken together with the carbons to which they are attached to for a cyclic moiety selected from: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycloalkyl, or substituted heterocycloalkyl;

All remaining substituents are as listed above.

Another aspect is a method for making a compound of Formula I herein, comprising the steps of: (i) reacting a proline derivative of formula VI:



VI

wherein,

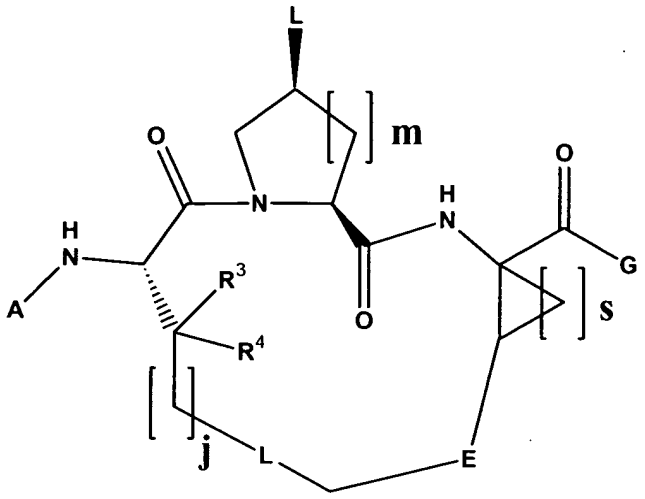
P is a nitrogen-protecting group (e.g., BOC);

L is a leaving group (e.g., halide, OMs);

R is optionally substituted alkyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl;

with a nucleophilic heterocyclic compound; and (ii) converting the resulting compound to a compound of Formula I as delineated herein.

Another aspect is a method for making a compound of Formula I herein, comprising the steps of: (i) reacting a compound of formula VII:



Formula VII

wherein,

L is a leaving group (e.g., halide, OMs);

A is a nitrogen protecting group (e.g., BOC); and

the remaining variables are as defined for formula I;

with a nucleophilic heterocyclic compound; and (ii) converting the resulting compound to a compound of Formula I as delineated herein.

In other aspects, the invention relates to a method for making a compound of any of the formulae delineated herein (e.g., Formulae I to VII with substituent variables as defined anywhere herein) or a pharmaceutically acceptable salt, ester or prodrug thereof, comprising the steps of: (i) reacting a proline derivative described herein (including that having a mesylate substituent) with a nucleophilic form (e.g., protonated or corresponding metal salt form) of a heterocyclic compound; and (ii) converting the resulting compound to a compound of any of the formulae delineated herein. In other aspects the method includes reacting any one or more intermediate compounds as

described herein, or includes any one or more steps or reagents or combination of transformations as specifically delineated in the examples and schemes herein.

In another aspect, the invention relates to a method of making a pharmceutical composition comprising combining a compound of any of the formulae herein or a pharmaceutically acceptable salt, ester or prodrug thereof, with a pharmaceutically acceptable carrier.

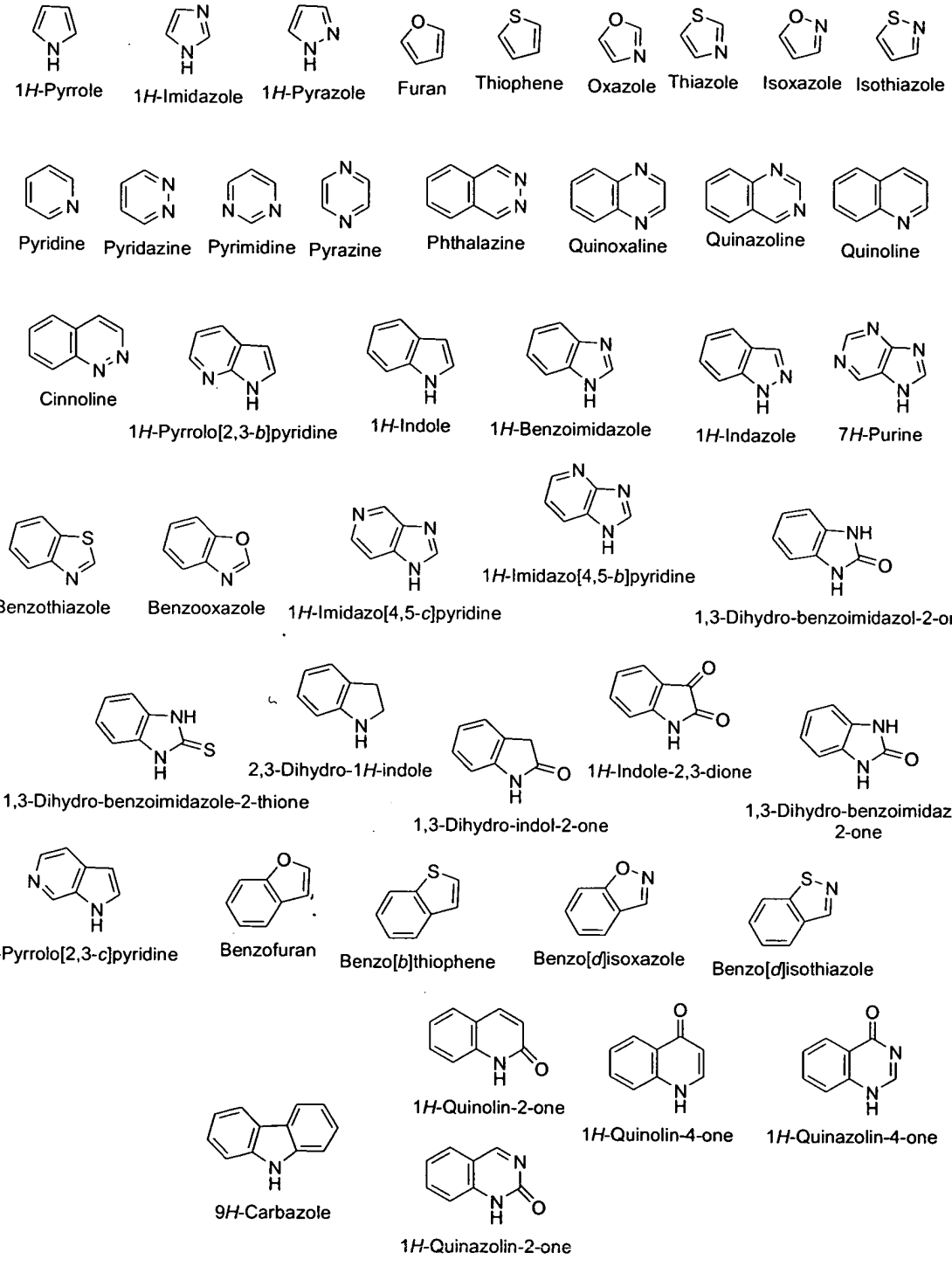
Another aspect is a compound of formulae VI or VII wherein L is OMs and A and the remaining variables are as defined for any of the formulae (e.g., I, II, III) herein.

DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In some embodiments , the compounds may be of any of the formulae delineated herein (including any substituent variables as defined anywhere delineated herein) wherein W is selected from the following aromatics, which may optionally be substituted:

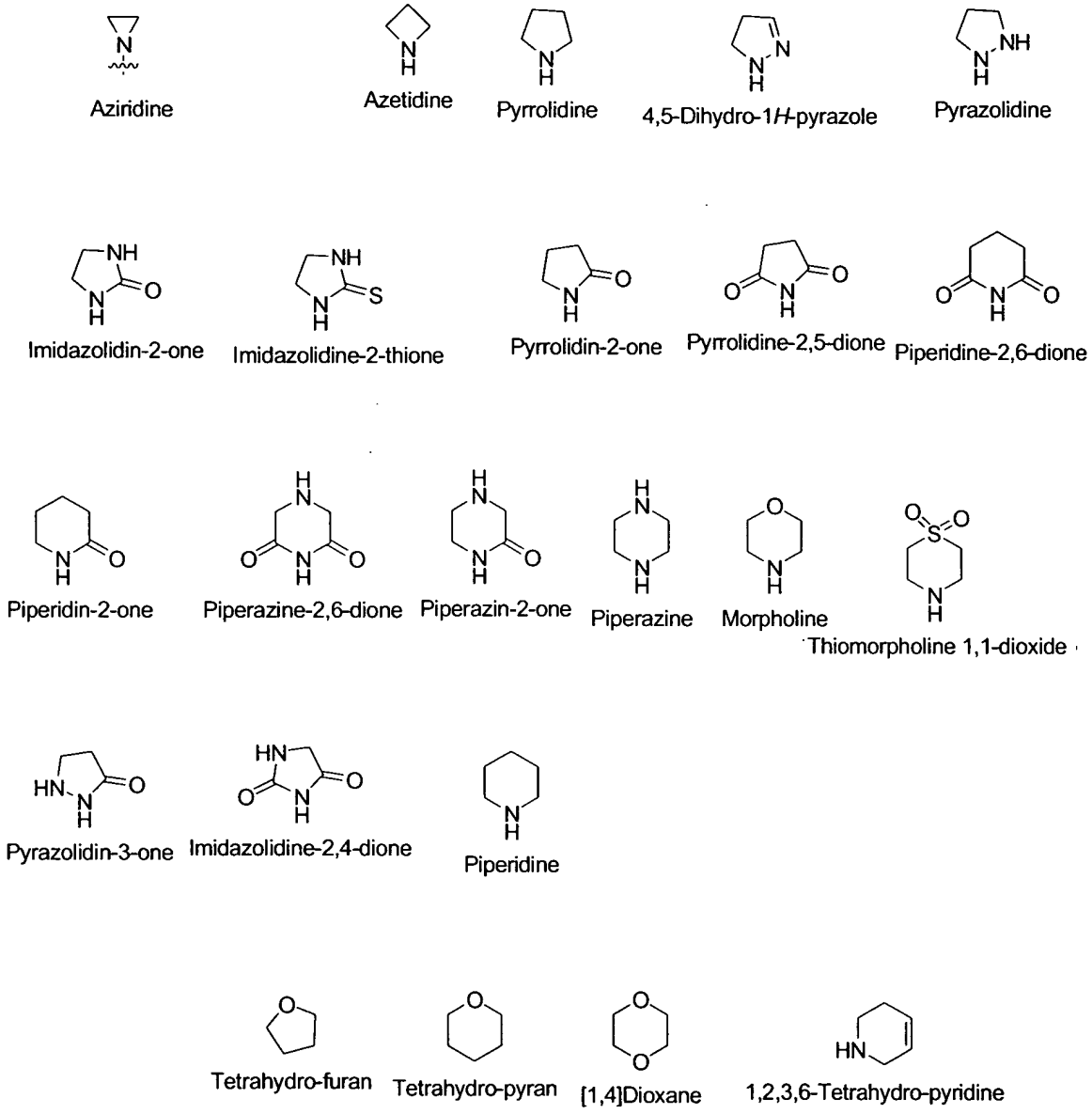
Aromatic



In other embodiments, the compounds may be of any of the formulae delineated herein (including any substituent variables as defined anywhere delineated herein)

wherein W is selected from the following non-aromatics, which may be optionally substituted:

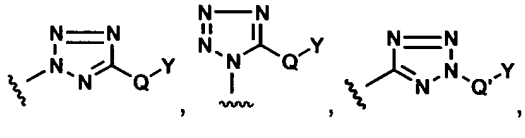
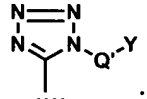
Non-Aromatic

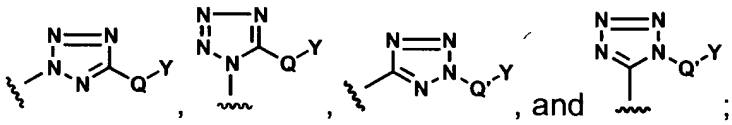


Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula II as described above where W is a tetrazole or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

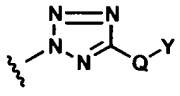
Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula III as described above wherein W is a tetrazole, or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

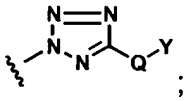
Exemplary tetrazolyl macrocyclic compounds and associated methods of the invention are disclosed in US Provisional Patent application no. _____(conversion of US 10/365,854), filed February 13, 2003. Representative subgenera of the invention include, but are not limited to:

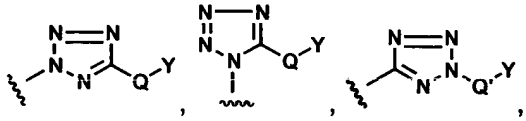
Compounds of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ,  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Q' is selected from the group consisting of: absent, –CH_2–, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl,

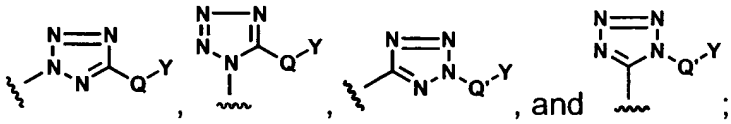
heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

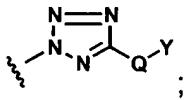
Compounds of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

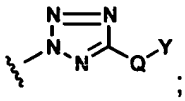
Compounds of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, –CH_2–, –O–, –NH–, –N(R^1)–, –S–, –S(O)$_2$–, and –(C=O)–; Q' is selected from the group consisting of:

absent, $-CH_2-$, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, –O–, –NH–, $-N(R^1)-$, –S–, $-S(O)_2-$, and –(C=O)–; Q' is selected from the group consisting of: absent, $-CH_2-$, and –NH–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

Compounds of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, –O–, –NH–, $-N(R^1)-$, –S–, $-S(O)_2-$, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen; and

Compounds of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; Q is selected from the group consisting of: absent, $-CH_2-$, –O–, –NH–, $-N(R^1)-$, –S–, $-S(O)_2-$, and –(C=O)–; Y is selected from the group consisting of: H, C_1–C_6 alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl,

heterocycloalkyl, and substituted heterocycloalkyl; j=3; m=s=1; and R^3 and R^4 are hydrogen.

Representative compounds of the invention include, but are not limited to, the following compounds:

TABLE 1

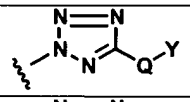
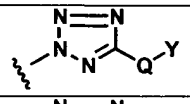
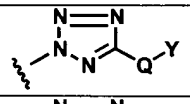
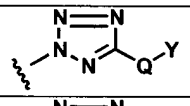
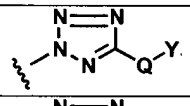
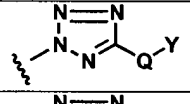
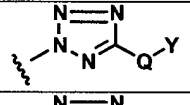
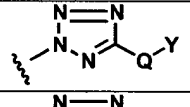
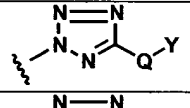
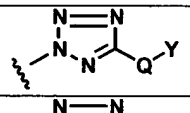
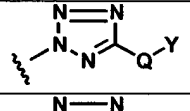
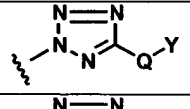
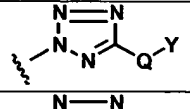
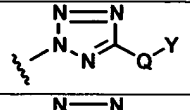
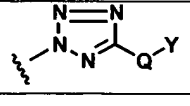
A	G	L	W	Q	Y	J	R^3, R^4
Compounds of Formula II, where m = s = 1							
tBOC	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	Absent		Absent	2-bromophenyl	3	$R^3 = R^4 = H$;
tBOC	OH	Absent		Absent	3-bromophenyl	3	$R^3 = R^4 = H$;
tBOC	OH	Absent		Absent	4-bromophenyl	3	$R^3 = R^4 = H$;
tBOC	OH	Absent		Absent	5-Bromo-2-thienyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	2-bromo-4-pyridyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	2-biphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-biphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-biphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-(3-thienyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-(p-trifluoromethoxy phenyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-(p-cyanophenyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-(3-thienyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		absent	4-(p-trifluoromethoxy phenyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-(p-cyanophenyl)phenyl	3	$R^3 = R^4 = H$;

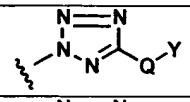
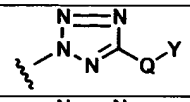
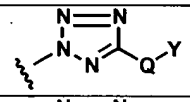
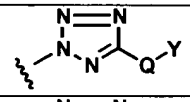
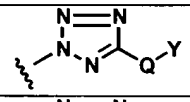
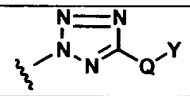
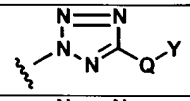
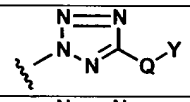
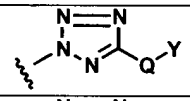
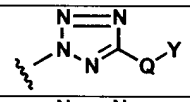
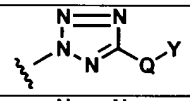
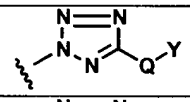
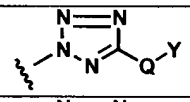
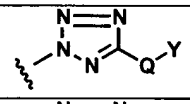
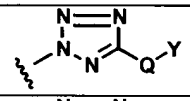
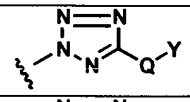
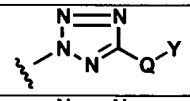
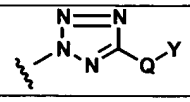
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
TBOC	OH	Absent		Absent	5-phenyl-2-thienyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	5-phenyl-3-pyridyl	3	$R^3 = R^4 = H$;
TBOC	OEt	Absent		Absent	3-chloro-4-hydroxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-hydroxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-bromo-4-hydroxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	2-methyl-4-bromophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-methyl-4-bromophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	n-propyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	n-butyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-ethoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-propoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-butoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-methoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3, 4-dimethoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-methoxy-1-naphthyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-phenoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	benzyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	p-phenylbenzyl	3	$R^3 = R^4 = H$;

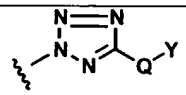
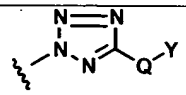
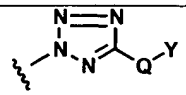
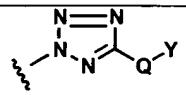
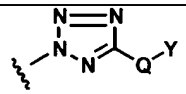
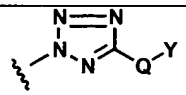
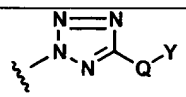
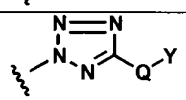
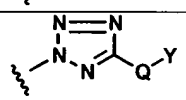
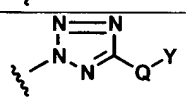
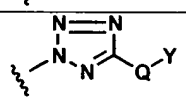
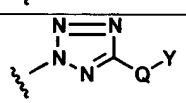
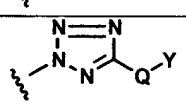
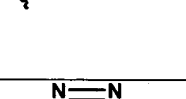
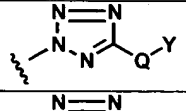
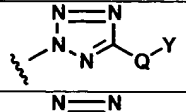
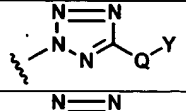
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
TBOC	OH	Absent		Absent	3-chlorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-fluorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-methoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-phenoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-benzyloxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-trifluormethylphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-bromophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-fluorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-methoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-ethoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-trifluoromethylphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	5-di(trifluoromethyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-(N, N-dimethylamino)-3, 5-di(trifluoromethyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	2, 4-dichlorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3, 5-dichlorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3, 4-dichlorophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	2-pyridyl	3	$R^3 = R^4 = H$;

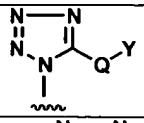
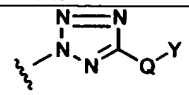
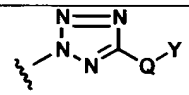
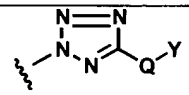
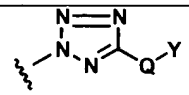
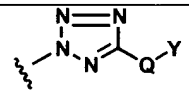
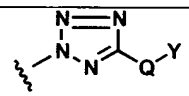
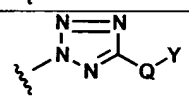
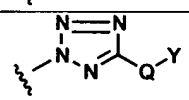
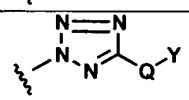
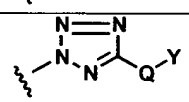
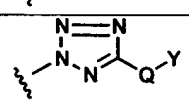
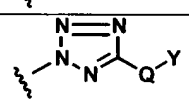
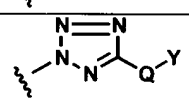
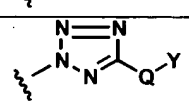
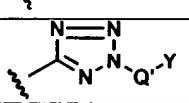
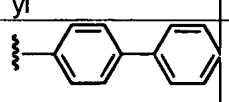
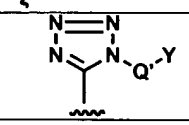
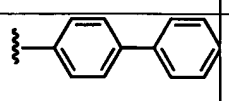
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
TBOC	OH	Absent		Absent	2-pyridyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-pyridyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-pyridyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-methoxy-3-bromophenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	4-(methylcyclopropane)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-(methylcyclopropane)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-methoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-ethoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-bromo-4-ethoxyphenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-(2-hydroxyethoxy)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-bromo-4-(2-hydroxyethoxy)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-(O-allyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-bromo-4-(O-allyl)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-(O-CH_2SCH_3)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Absent	3-chloro-4-(O-CH_2SCH_3)phenyl	3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Q' = $-CH_2-$		3	$R^3 = R^4 = H$;
TBOC	OH	Absent		Q' = $-CH_2-$		3	$R^3 = R^4 = H$;

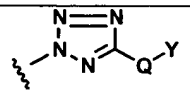
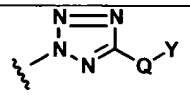
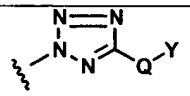
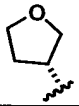
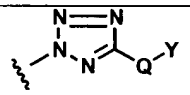
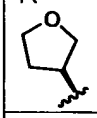
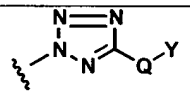
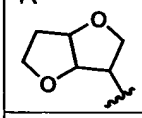
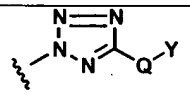
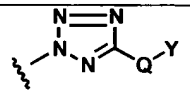
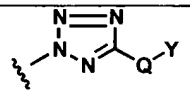
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
–(C=O)–O–R^1 wherein R^1 = cyclopentyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 wherein R^1 = cyclobutyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 wherein R^1 = cyclohexyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 wherein R^1 = 	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 wherein R^1 = 	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 wherein R^1 = 	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–R^1 wherein R^1 = cyclopentyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–(C=O)–NH–R^1 wherein R^1 = cyclopentyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;

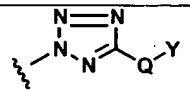
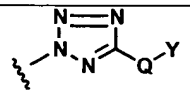
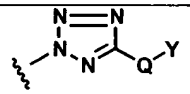
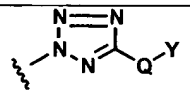
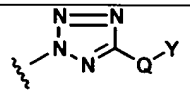
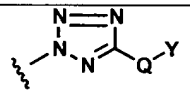
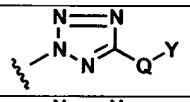
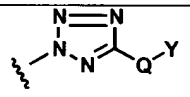
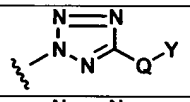
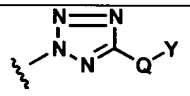
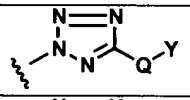
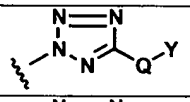
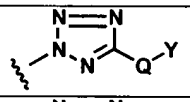
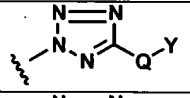
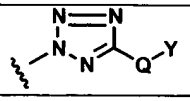
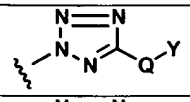
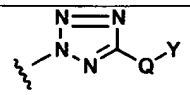
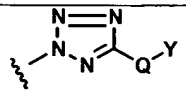
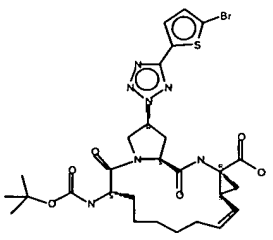
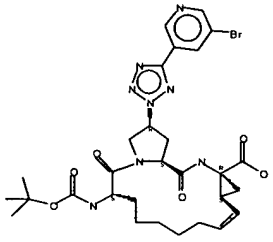
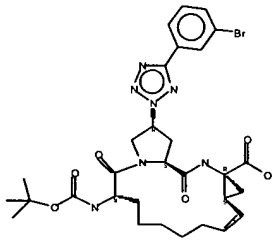
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
–(C=S)–NH–R^1 wherein R^1 = cyclopentyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
–$S(O)_2$–R^1 wherein R^1 = cyclopentyl	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	–O–CH_2–cyclopentyl	Absent		Absent	phenyl	3	R3 = R4 = H;
tBOC	–NHS(O)$_2$–CH_2–cyclopentyl	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	–(C=O)–CH_2–cyclopentyl	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	–(C=O)–O–CH_2–cyclopentyl	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	–(C=O)–OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	–(C=O)–NH—CH$_2$–cyclopentyl	Absent		Absent	phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	–(C=O)CH_2–		Absent	phenyl	1	$R^3 = R^4 = H$;
tBOC	OH	–CH(CH_3)CH_2–		Absent	phenyl	1	R^3 = methyl, $R^4 = H$;
tBOC	OH	–O–		Absent	phenyl	0	R^3 = methyl $R^4 = H$;
tBOC	OH	–S–		Absent	phenyl	0	R^3 = methyl, $R^4 = H$;
tBOC	OH	–S(O)–		Absent	phenyl	0	R^3 = methyl, $R^4 = H$;
tBOC	OH	–$S(O)_2$–		Absent	phenyl	0	R^3 = methyl, $R^4 = H$;
tBOC	OH	–SCH_2 CH_2–		Absent	phenyl	0	$R^3 = R^4 = CH_3$;

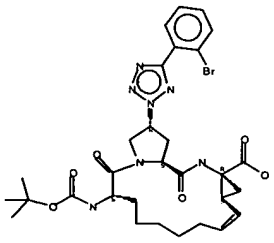
TABLE 1							
A	G	L	W	Q	Y	J	R^3, R^4
tBOC	OH	$-CF_2CH_2-$		Absent	phenyl	1	$R^3 = R^4 = H$;
tBOC	OH	$-CFHCH_2-$		Absent	phenyl	1	$R^3 = R^4 = H$;
Compounds of Formula III, where m = s = 1							
tBOC	OH	Absent		Absent	phenyl	3	$R^3 = R^4 = H$.

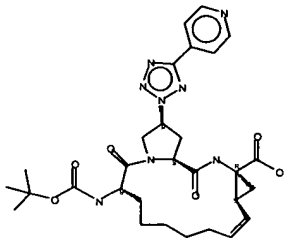
The following additional tetrazolyl macrocyclic molecules of the invention were made by the methods and procedures described herein. While stereochemistry is shown, the invention is not limited to the stereochemistry depicted. Those of ordinary skill in the art will readily appreciate that other isomers of these compounds are also within the scope of the invention.

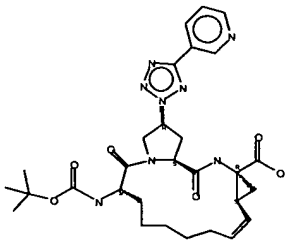


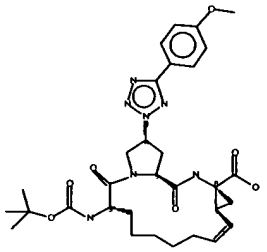
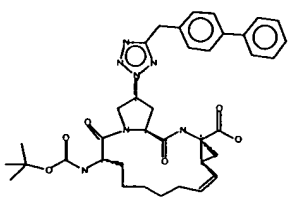
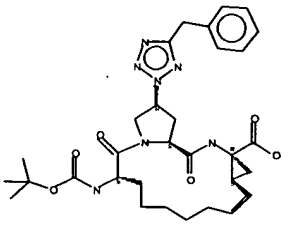
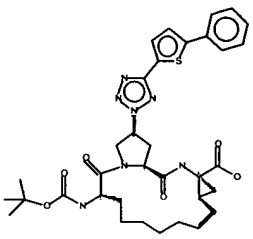
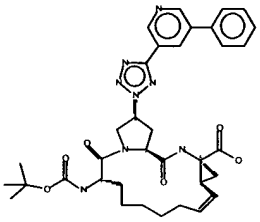
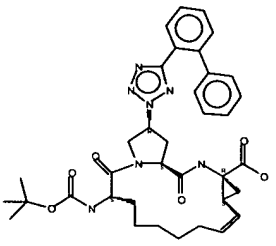
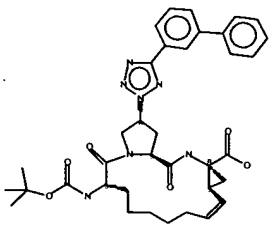
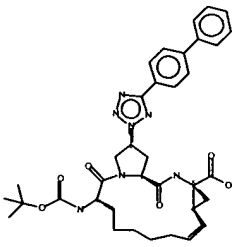
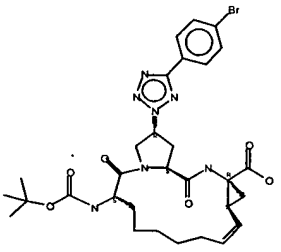
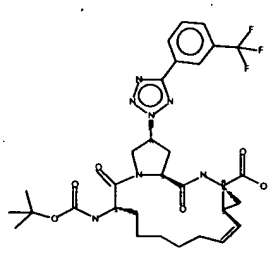
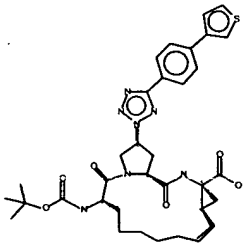
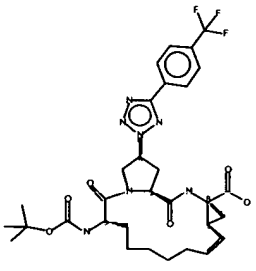


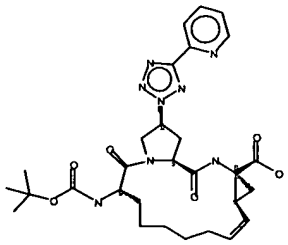
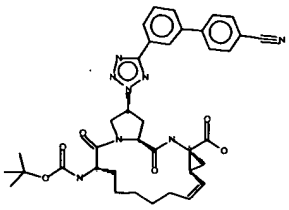
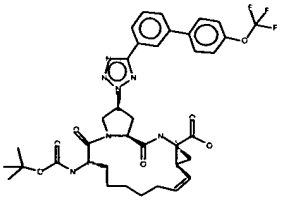
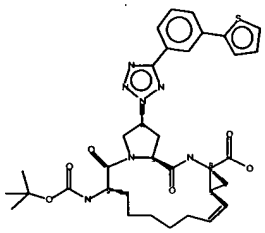
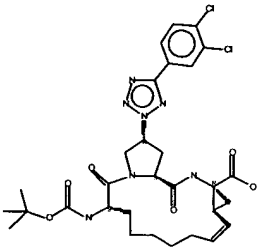
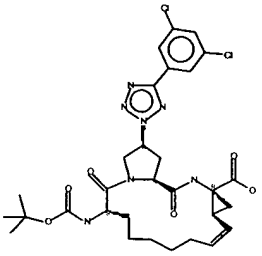
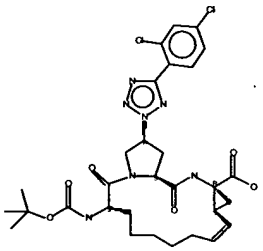
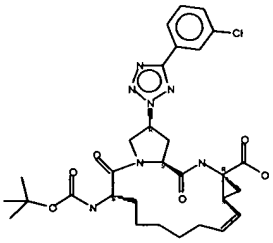
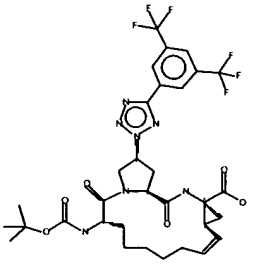
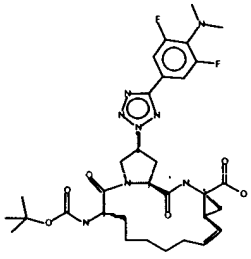
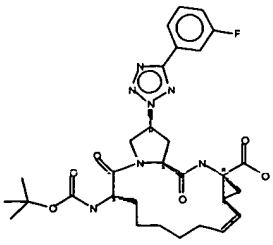
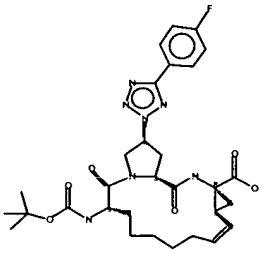


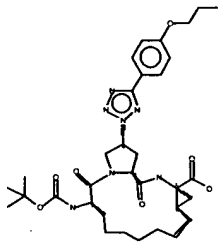
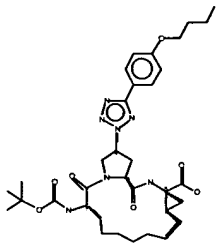
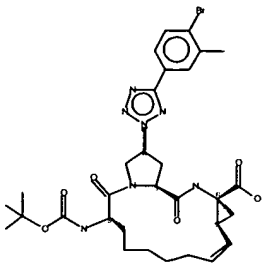
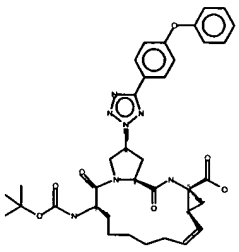
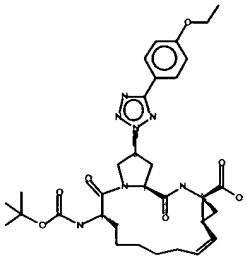
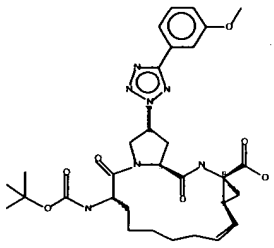
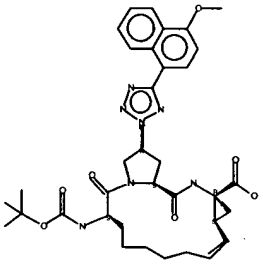
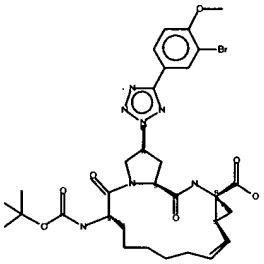
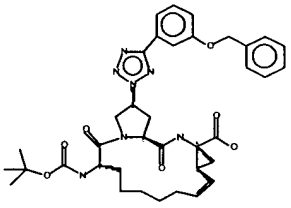
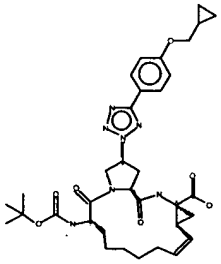
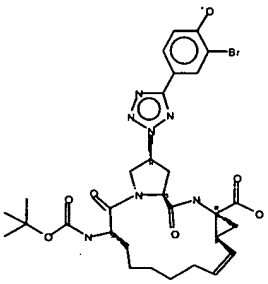
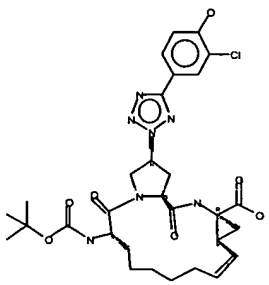


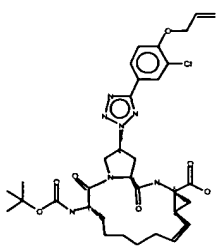
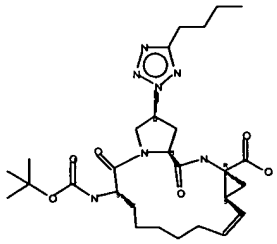
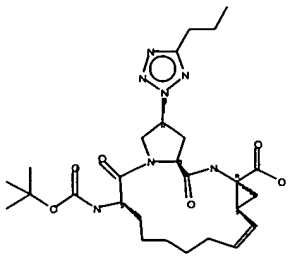
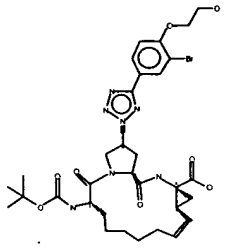
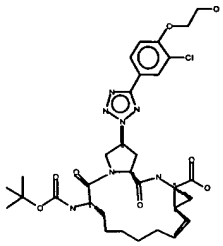
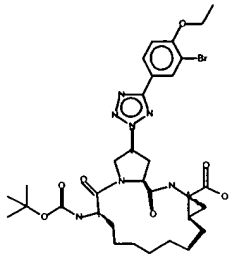
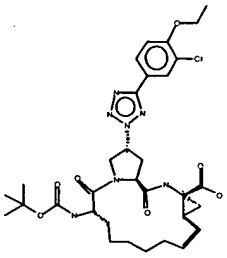
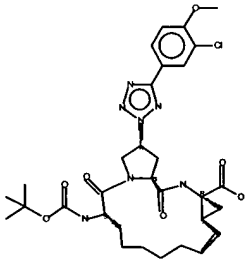
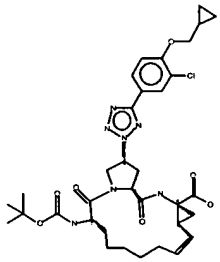
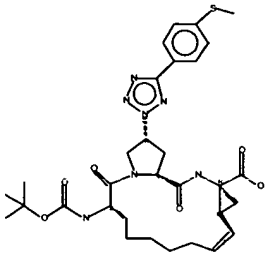
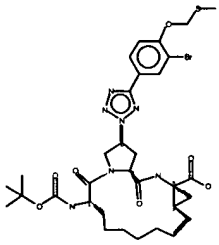
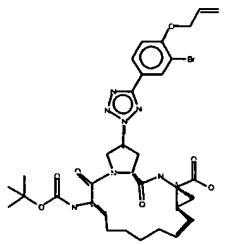


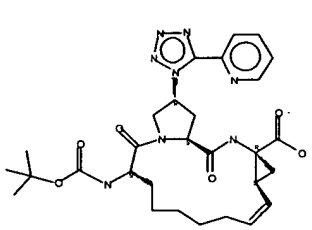
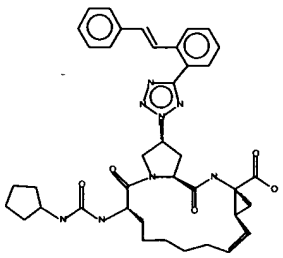
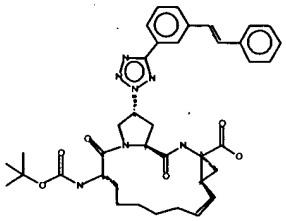
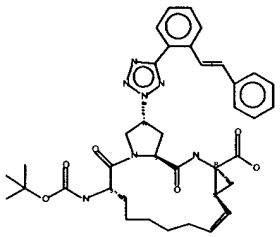
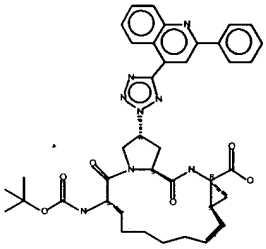
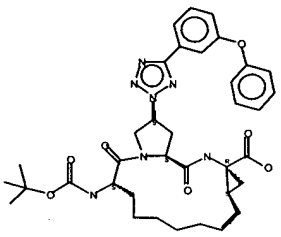
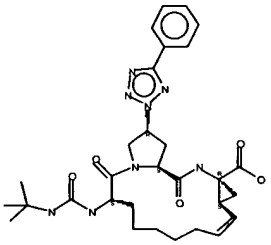
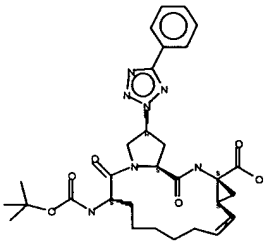
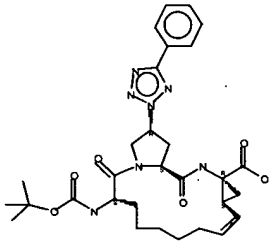


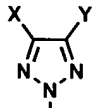
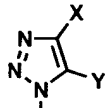










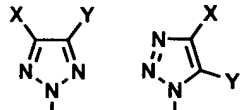
Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula II as described above where W is a triazole or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula III as described above

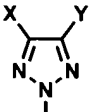
where W is a triazole or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

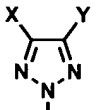
Exemplary triazole macrocyclic compounds and associated methods of the invention are disclosed in US Provisional Patent application no. _____(conversion of US 10/360,947), filed February 7, 2003. Representative subgenera of the invention include, but are not limited to:

A compound of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is selected from the group consisting of:,  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

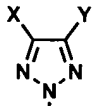
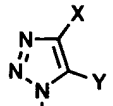
A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is selected from the group consisting of:  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,

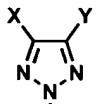
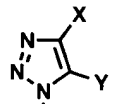
heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

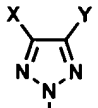
A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to

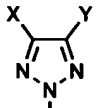
which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula III, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is selected from the group consisting of:,  , and  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is selected from the group consisting of:  or  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form

a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen;

A compound of Formula II, wherein A is -(C=O)-O-R^1, R^1 is selected from the group consisting of H, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, substituted C_3–C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen; and

A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; W is  ; X and Y are independently selected from the group consisting of: H, halogen, C_1–C_6 alkyl, C_3–C_{12} cycloalkyl, –CH_2-alkylamino, –CH_2-dialkylamino, –CH_2-arylamino, –CH_2-diarylamino, –(C=O)-alkylamino, –(C=O)-dialkylamino, –(C=O)-arylamino, –(C=O)-diarylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyl, and substituted heterocycloalkyl; in the alternative, X and Y taken together with the carbon atoms occupying the 4 and 5 positions of the triazole ring, to which X and Y are attached, form a cyclic moiety selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; j=3; m=s=1; and R^3 and R^4 are hydrogen.

Representative compounds of the invention include, but are not limited to, the following compounds:

TABLE 2
Compounds of Formula II where m = s= 1

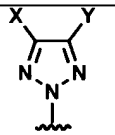
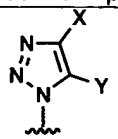
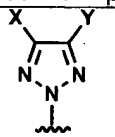
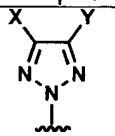
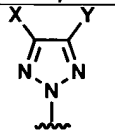
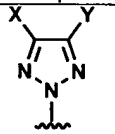
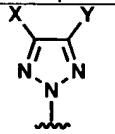
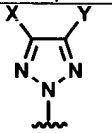
A	G	L	W	j	R^3 , R^4
tBOC	OH	absent	 X = Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = Y = phenyl	3	$R^3 = R^4 = H$.
tBOC	OH	absent	 X = n-propyl Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = m-methoxyphenyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = m-bromophenyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 1-napthyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 2-thienyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 3-thienyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;

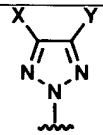
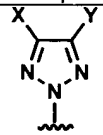
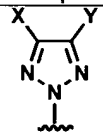
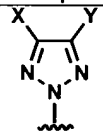
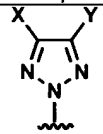
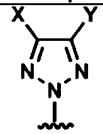
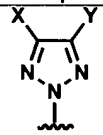
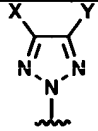
TABLE 2 Compounds of Formula II where m = s= 1					
A	**G**	**L**	**W**	**j**	**R^3 , R^4**
tBOC	OH	absent	 X = 4-pyrazolyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 3-pyridyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 2-pyridyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 2-thiazolyl; Y = p-methoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = benzyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = n-butyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = n-propyl; Y = n-propyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 4-(N, N-dimethylamino)phenyl; Y = phenyl	3	$R^3 = R^4 = H$;

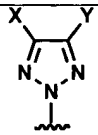
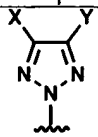
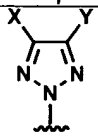
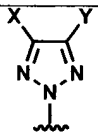
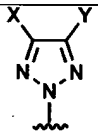
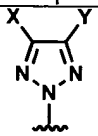
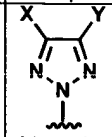
TABLE 2 Compounds of Formula II where m = s= 1					
A	**G**	**L**	**W**	**j**	**R^3, R^4**
tBOC	OH	absent	 X = (N, N-diethylamino)methyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = N, N-diethylaminocarbonyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = m-chlorophenyl; Y = 4-ethoxyphenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	 X = 2-phenylethenyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent	Benzotriazole	3	$R^3 = R^4 = H$;
tBOC	OH	absent	5, 6-methylbenzotriazole	3	$R^3 = R^4 = H$; and
tBOC	OH	absent	 X = N-ethylaminocarbonyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1; wherein R^1 = cyclopentyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1; wherein R^1 = cyclobutyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;

TABLE 2
Compounds of Formula II where m = s= 1

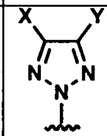
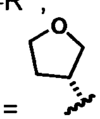
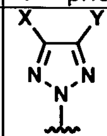
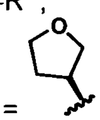
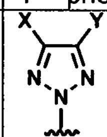
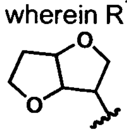
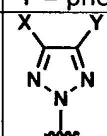
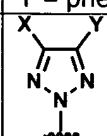
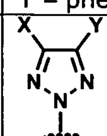
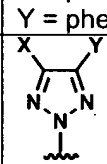
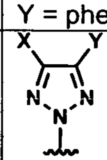
A	G	L	W	j	R^3, R^4
–(C=O)–O–R^1 ; wherein R^1 = cyclohexyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 ; wherein R^1 = 	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 ; wherein R^1 = 	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–O–R^1 ; wherein R^1 = 	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–R^2 ; wherein R^2 = cyclopentyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–(C=O)–NH–R^2 ; wherein R^2 = cyclopentyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
wherein R^2 = cyclopentyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
–$S(O)_2$–R^2 ; wherein R^2 = cyclopentyl	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;

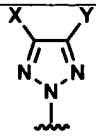
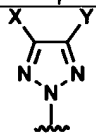
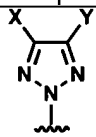
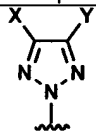
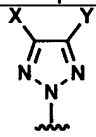
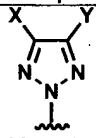
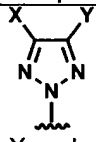
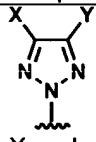
TABLE 2 Compounds of Formula II where m = s= 1					
A	G	L	W	j	R^3 , R^4
–(C=O)–O–R^1 ; wherein R^1 = cyclopentyl	–O–phenethyl	absent	 X = phenyl; Y = phenyl	3	R3 = R4 = H;
–(C=O)–O–R^1 ; wherein R^1 = cyclopentyl	–NH–phenethyl	absent	 X = phenyl; Y = phenyl	3	R3 = R4 = H;
–(C=O)–O–R^1 wherein R^1 = cyclopentyl	–$NHS(O)_2$–phenethyl	absent	 X = phenyl; Y = phenyl	3	R3 = R4 = H;
–(C=O)–O–R^1 ; wherein R^1 = cyclopentyl	–(C=O)–OH	absent	 X = phenyl; Y = phenyl	3	R^3 = R^4 = H;
–(C=O)–O–R^1 ; wherein R^1 = cyclopentyl	–(C=O)–O–phenethyl	absent	 X = phenyl; Y = phenyl	3	R^3 = R^4 = H;
–(C=O)–O–R^1 ; wherein R^1 = cyclopentyl	–(C=O)–NH–phenethyl	absent	 X = phenyl; Y = phenyl	3	R^3 = R^4 = H;
–(C=O)–O–R^1 wherein R^1 = cyclopentyl	–(C=O)–NH–$S(O)_2$–benzyl	absent	 X = phenyl; Y = phenyl	3	R^3 = R^4 = H;
tBOC	OH	–(C=O)CH_2–	 X = phenyl; Y = phenyl	1	R^3 = R^4 = H;

TABLE 2
Compounds of Formula II where m = s= 1

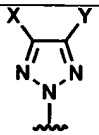
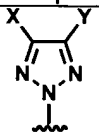
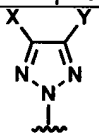
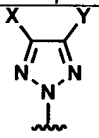
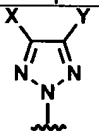
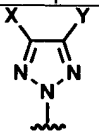
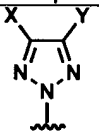
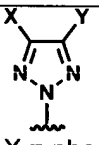
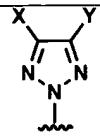
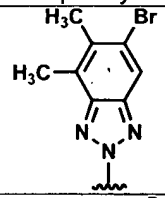
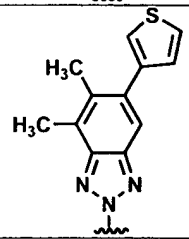
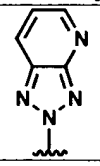
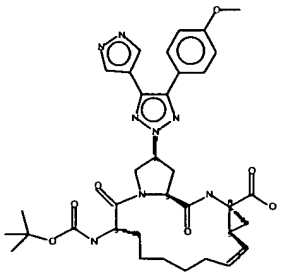
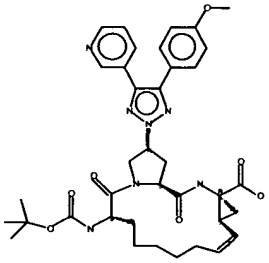
A	G	L	W	j	R^3 , R^4
tBOC	OH	–CH(CH_3)CH_2–	 X = phenyl; Y = phenyl	1	R^3 = methyl R^4 = H
tBOC	OH	–O–	 X = phenyl; Y = phenyl	0	R^3 = methyl; R^4 = H;
tBOC	OH	–S–	 X = phenyl; Y = phenyl	0	R^3 = methyl; R^4 = H;
tBOC	OH	–S(O)–	 X = phenyl; Y = phenyl	0	R^3 = methyl; R^4 = H;
tBOC	OH	–$S(O)_2$–	 X = phenyl; Y = phenyl	0	R^3 = methyl; R^4 = H;
tBOC	OH	–SCH_2 CH_2–	 X = phenyl; Y = phenyl	0	R^3 = R^4 = CH_3;
tBOC	OH	–CF_2C H_2–	 X = phenyl; Y = phenyl	1	R^3 = R^4 = H;
tBOC	OH	–CFH CH_2–	 X = phenyl; Y = phenyl	1	R^3 = R^4 = H;

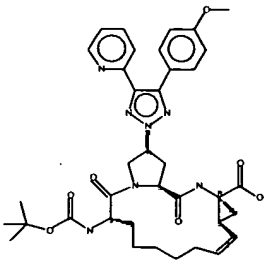
TABLE 2
Compounds of Formula II where m = s= 1

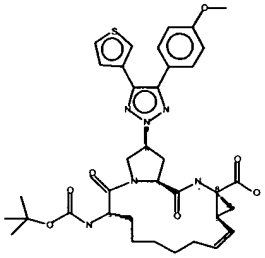
A	G	L	W	j	R^3 , R^4
tBOC	OH	absent	 X = phenyl; Y = phenyl	3	$R^3 = R^4 = H$;
tBOC	OH	absent		3	$R^3 = R^4 = H$;
tBOC	OH	absent		3	$R^3 = R^4 = H$;
tBOC	OH	absent		3	$R^3 = R^4 = H$.

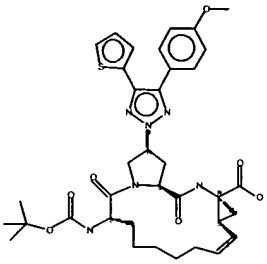
The following additional triazole macrocyclic molecules of the invention were made by the methods and procedures described herein. While stereochemistry is shown, the invention is not limited to the stereochemistry depicted. Those of ordinary skill in the art will readily appreciate that other isomers of these compounds are also within the scope of the invention.

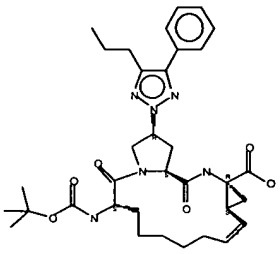


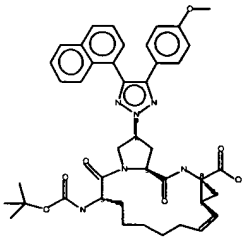


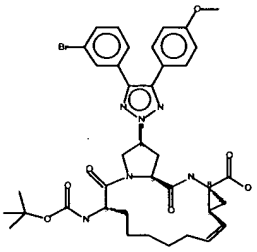


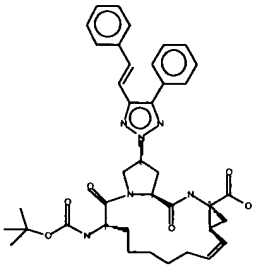


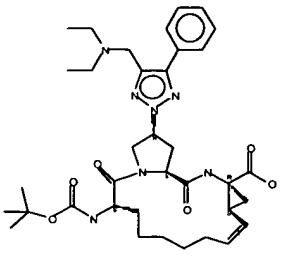


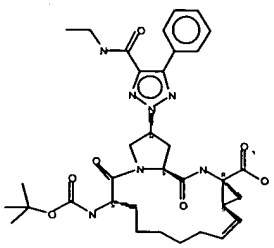


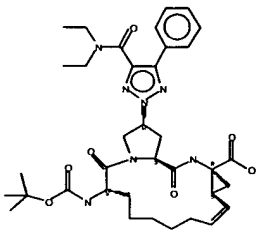


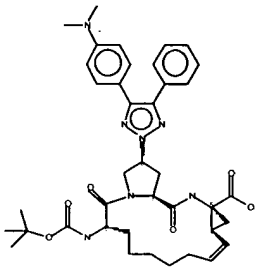


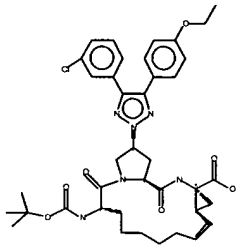


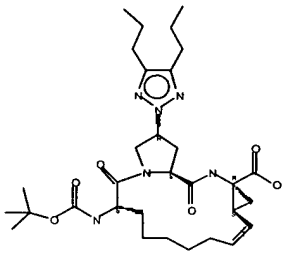


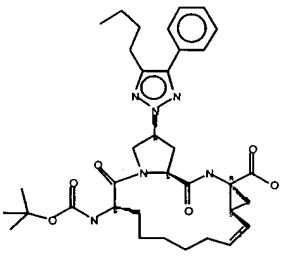


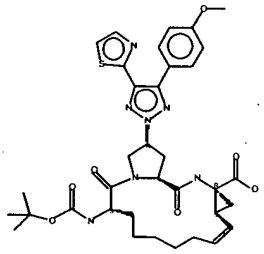


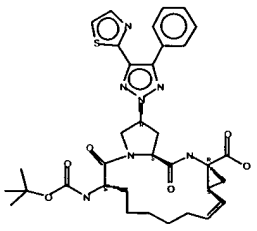


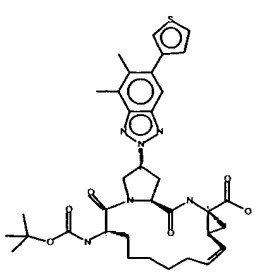


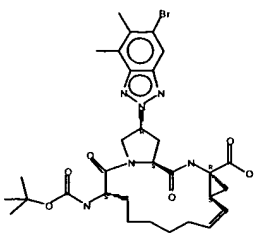


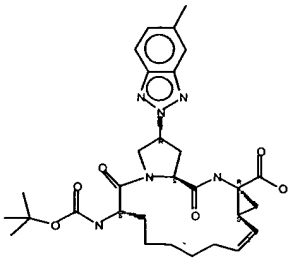


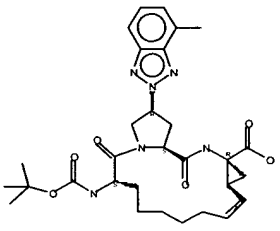


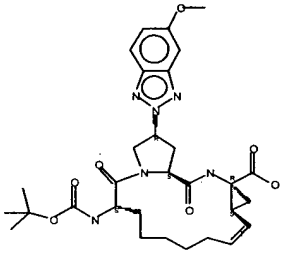


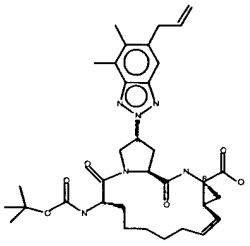


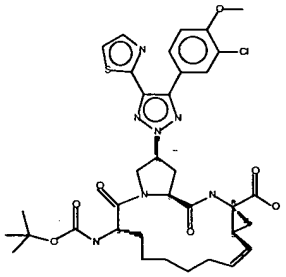


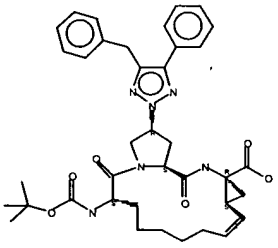


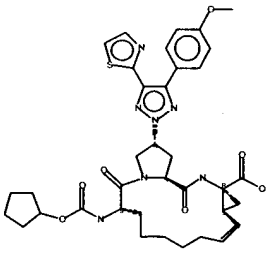


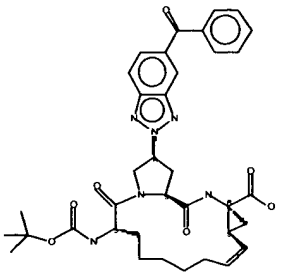


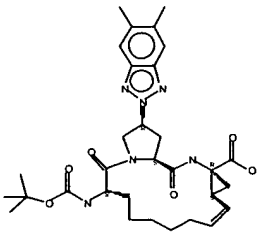


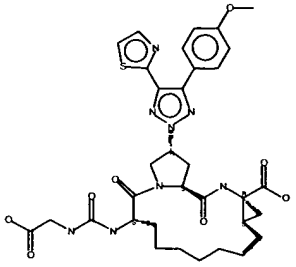


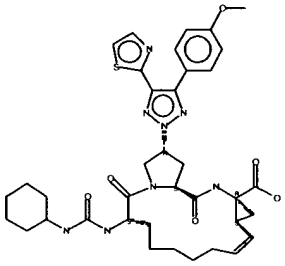


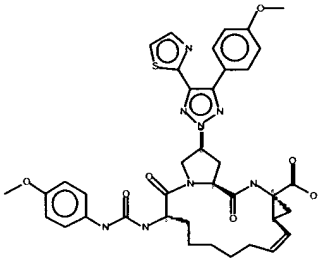


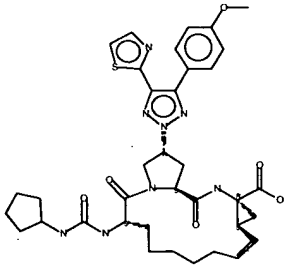


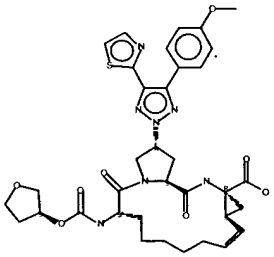


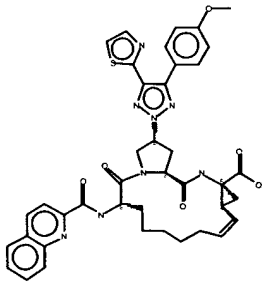


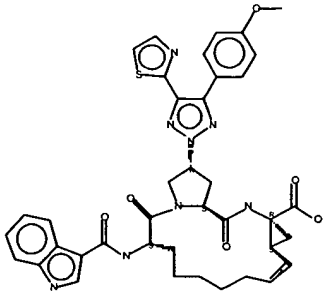


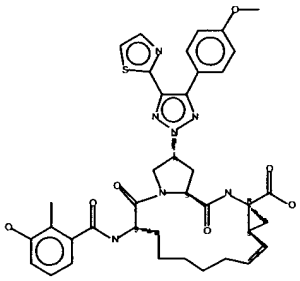


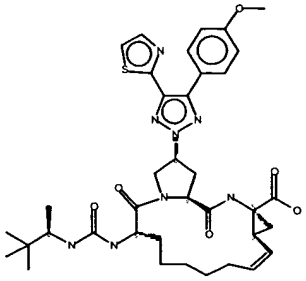


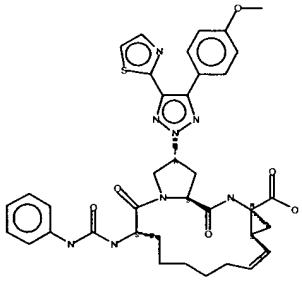


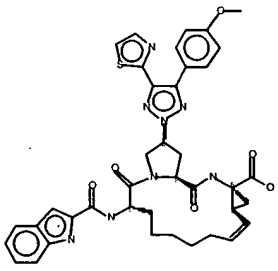


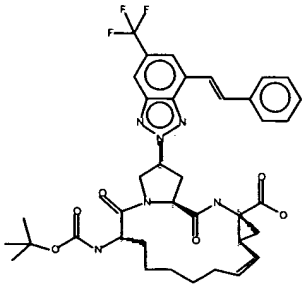


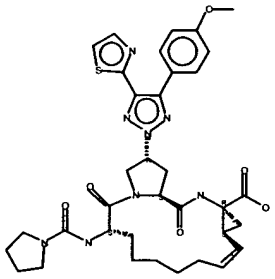


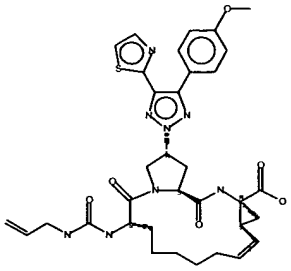


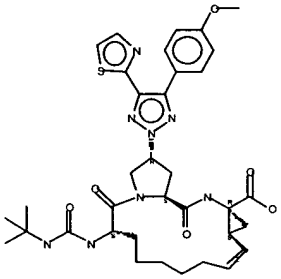


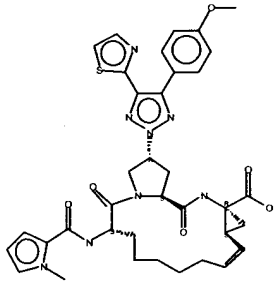


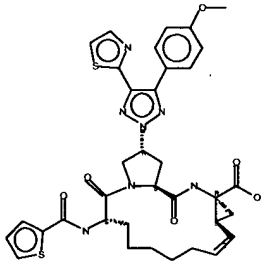


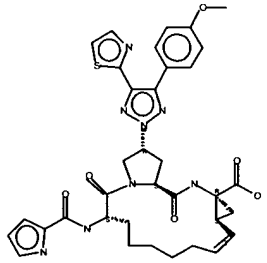


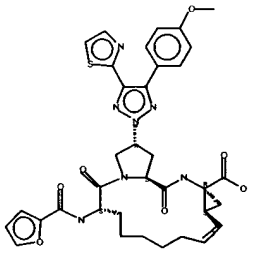


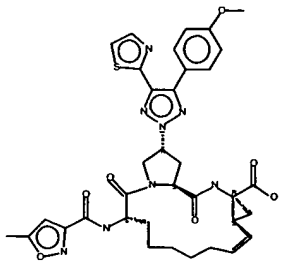
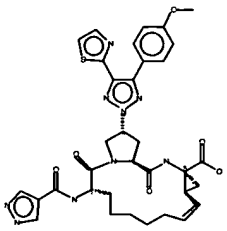
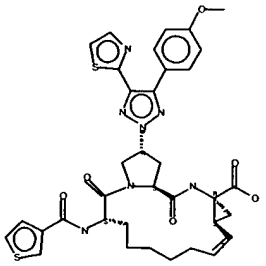
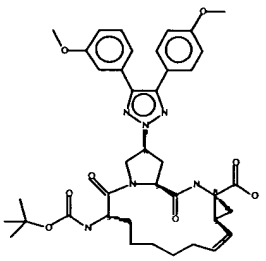
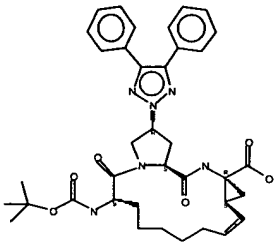
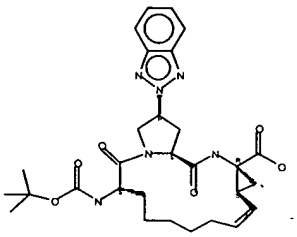
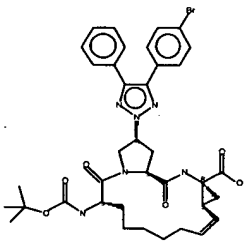










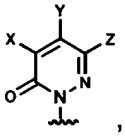








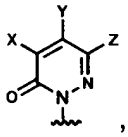
Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula II as described above where W is a pyridazinone or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

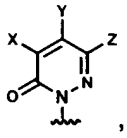
Another embodiment of the invention is a compound, or a pharmaceutically acceptable salt, ester or prodrug thereof, represented by Formula III as described above

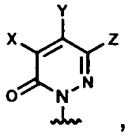
where W is a pyridazinone or derivative thereof, in combination with a pharmaceutically acceptable carrier or excipient.

Exemplary pyridazinone macrocyclic compounds and associated methods of the invention are disclosed in US Provisional Patent application no. _____(conversion of US 10/384,120), filed March 7, 2003. Representative subgenera of the invention include, but are not limited to:

A compound of Formula II, wherein A is -(C=O)-O-R^1 ; G is hydroxyl; L is absent; ; j=3; m=s=1; W=  , and R^3 and R^4 are hydrogen;

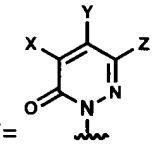
A compound of Formula II, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; j=3; m=s=1; W=  , and R^3 and R^4 are hydrogen;

A compound of Formula III, wherein A is -(C=O)-O-R^1; L is absent; j=3; m=s=1; W=  , and R^3 and R^4 are hydrogen; and

A compound of Formula III, wherein A is -(C=O)-O-*tert*-butyl; G is hydroxyl; L is absent; j=3; m=s=1; W=  , and R^3 and R^4 are hydrogen.

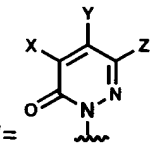
Representative compounds of the invention include, but are not limited to, the following compounds:

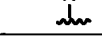
TABLE 3

compounds of formula II where W=  and m = s= 1

A	G	L	X,Y	Z	j	R^3, R^4
TBOC	OEt	absent	X = Y = bromo	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OEt	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;

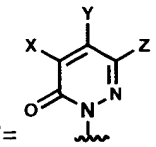
TABLE 3

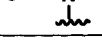


compounds of formula II where W=  and m = s= 1

A	G	L	X,Y	Z	j	R^3 , R^4
TBOC	OH	absent	X = Y = 4-(N, N-dimethylamino)phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = 4-(trifluoromethoxy)phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = 4-(methanesulfonyl)phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = 4-(cyano)phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = 3-pyridyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = 4-(morpholin-4-yl-methanonyl)phenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = bromo	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X and Y taken together = phenyl	Z = 4-methoxyphenyl	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X and Y taken together = phenyl	Z = 4-chlorophenyl	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = 4-fluorophenyl Y = hydrogen	Z = phenyl	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = hydrogen Y = 1-piperidyl	Z = phenyl	3	R^3 = R^4 = hydrogen;
TBOC	OEt	absent	X = hydrogen Y = bromo	Z = phenyl	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = hydrogen Y = thiophen-3-yl	Z = phenyl	3	R^3 = R^4 = hydrogen;
TBOC	OEt	absent	X = bromo Y = pyrrolid-1-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = thiophen-3-yl Y = pyrrolid-1-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OEt	absent	X = bromo Y = azido	Z = hydrogen	3	R^3 = R^4 = hydrogen;

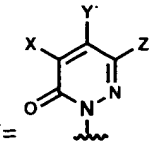
TABLE 3



compounds of formula II where W=  and m = s= 1

A	G	L	X,Y	Z	j	R^3, R^4
TBOC	OEt	absent	X = thiophen-3-yl Y = azido	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = thiophen-3-yl Y = azido	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = thiophen-3-yl Y = tetrazol-2-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = mercapto–2–pyrimidine	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = bromo Y = mercapto–2–pyrimidine	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = thiophen-3-yl Y = mercapto–2–pyrimidine	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = thiazol-2-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = Y = imidazol-1-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X = 2-(cyclopropylamino)-thiazol-4-yl Y = 4-methoxyphenyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	absent	X and Y taken together = 6-methoxy-isoquinolinyl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 Wherein R^1 = cyclopentyl	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 wherein R^1 = cyclobutyl	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 wherein R^1 = cyclohexyl	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;

TABLE 3

compounds of formula II where W=  and m = s= 1

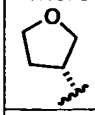
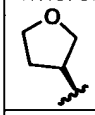
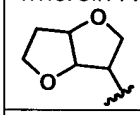
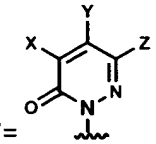
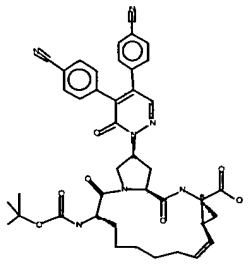
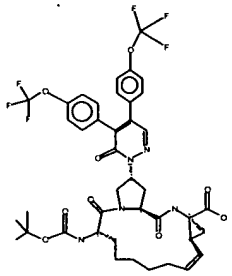
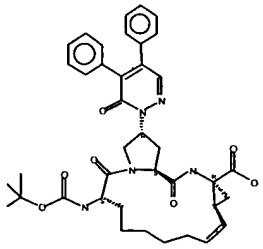
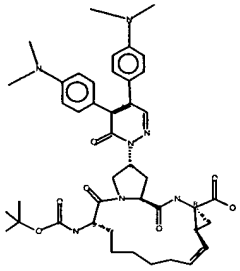
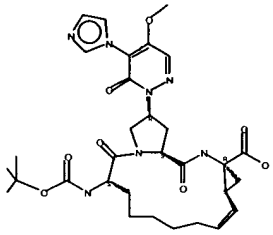
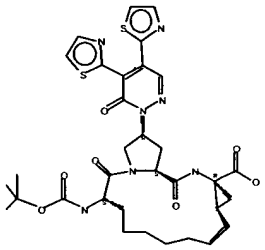
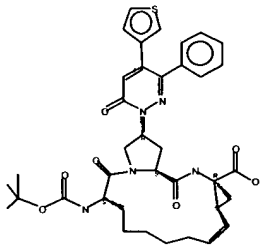
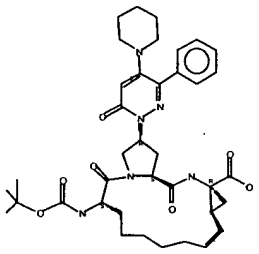
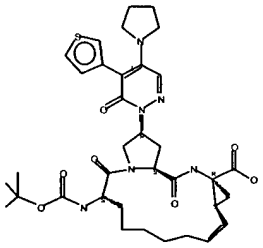
A	G	L	X,Y	Z	j	R^3, R^4
–(C=O)–O–R^1 wherein R^1 = 	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 wherein R^1 = 	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 wherein R^1 = 	OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
TBOC	OH	–(C=O)CH_2–	X = Y = thiophen-3-yl	Z = hydrogen	1	R^3 = R^4 = hydrogen;
TBOC	OH	–$CH(CH_3)CH_2$–	X = Y = thiophen-3-yl	Z = hydrogen	1	R^3 = methyl R^4 = hydrogen
TBOC	OH	–O–	X = Y = thiophen-3-yl	Z = hydrogen	0	R^3 = methyl and R^4 = hydrogen
TBOC	OH	–S–	X = Y = thiophen-3-yl	Z = hydrogen	0	R^3 = methyl and R^4 = hydrogen
TBOC	OH	–S(O)–	X = Y = thiophen-3-yl	Z = hydrogen	2	R^3 = methyl and R^4 = hydrogen
TBOC	OH	–$S(O)_2$–	X = Y = thiophen-3-yl	Z = hydrogen	2	R^3 = methyl and R^4 = hydrogen
TBOC	OH	–SCH_2CH_2–	X = Y = thiophen-3-yl	Z = hydrogen	0	R^3 = R^4 = CH_3;
TBOC	OH	–CF_2CH_2–	X = Y = thiophen-3-yl	Z = hydrogen	1	R^3 = R^4 = hydrogen;
TBOC	OH	–$CFHCH_2$–	X = Y = thiophen-3-yl	Z = hydrogen	1	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–O–phenethyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–NH–phenethyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;

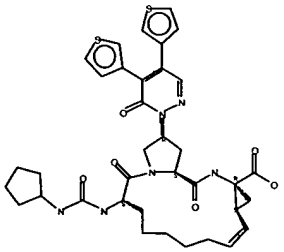
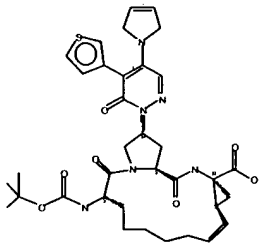
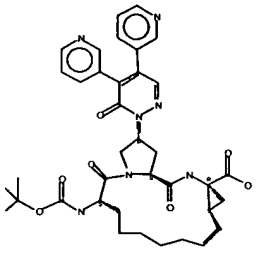
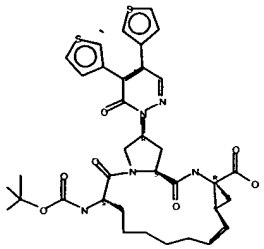
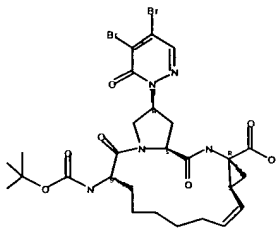
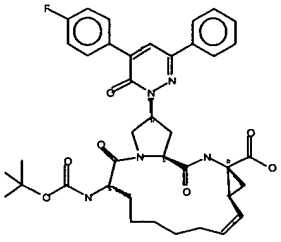
TABLE 3

compounds of formula II where W=  and m = s= 1

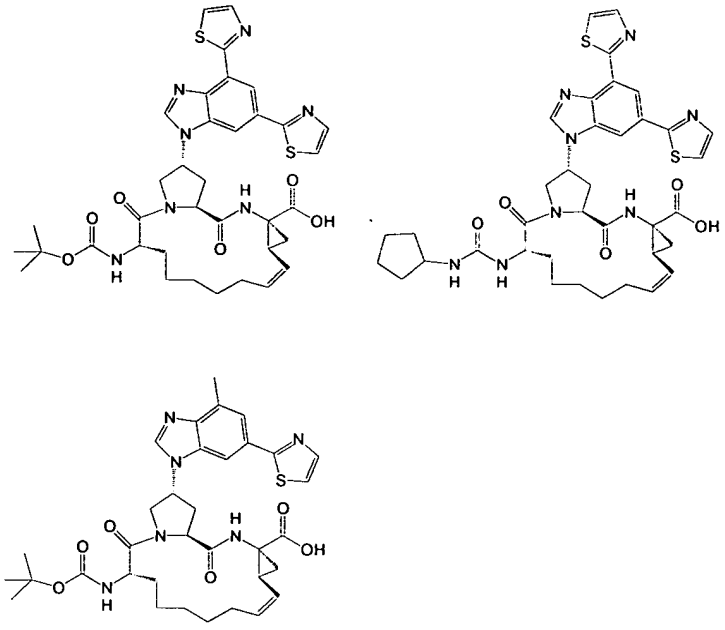
A	G	L	X,Y	Z	j	R^3, R^4
–(C=O)–O–R^1 R^1 = cyclopentyl	–NHS(O)$_2$–phenethyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–(C=O)–OH	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–(C=O)–O–phenethyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–(C=O)–NH–phenethyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen;
–(C=O)–O–R^1 R^1 = cyclopentyl	–(C=O)–NH–S(O)$_2$–benzyl	absent	X = Y = thiophen-3-yl	Z = hydrogen	3	R^3 = R^4 = hydrogen.

The following additional pyridazinone macrocyclic molecules of the invention were made by the methods and procedures described herein. While stereochemistry is shown, the invention is not limited to the stereochemistry depicted. Those of ordinary skill in the art will readily appreciate that other isomers of these compounds are also within the scope of the invention.

Additional compounds of the invention are those of formula I, II or II, wherein W is a substituted benzimidazolyl, including those wherein the benzimidazolyl is substituted with 1 or 2 heteroaryl groups, each of which may be independently substituted. Examples of such compounds include:



According to an alternate embodiment, the pharmaceutical compositions of the present invention may further contain other anti-HCV agents. Examples of anti-HCV agents include, but are not limited to, α-interferon, β-interferon, ribavirin, and amantadine.

According to an additional alternate embodiment, the pharmaceutical compositions of the present invention may further contain other HCV protease inhibitors.

According to yet another alternate embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, and internal ribosome entry site (IRES).

According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering to said subject an anti-HCV virally effective amount of the pharmaceutical compounds or compositions of the present invention. The methods can further include administration of an additional therapeutic agent, including another antiviral agent or an anti-HCV agent. The additional agent can be co-administered, concurrently administered or

sequentially administered with the compound or composition delineated herein. The methods herein can further include the step of identifying that the subject is in need of treatment for hepatitis C infection. The identification can be by subjective (e.g., health care provider determination) or objective (e.g., diagnostic test) means.

All references, including patents, patent publications, articles, texts, etc. disclosed throughout this specification are hereby incorporated by reference in their entirety.

Definitions

The following definitions of various terms and phrases used to describe the invention are consistent with their normal use in the art and apply to the terms as they are used throughout this specification and claims unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "C_x-C_y," as used herein, is used in conjunction with the name of a carbon-containing group to indicate that the group contains from x to y carbon atoms where x and y are whole numbers.

The term "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "alkyl," as used herein, refers to saturated, straight- or branched-chain hydrocarbon radicals. Examples include, but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, neopentyl, n-hexyl, octyl, decyl, dodecyl radicals.

The term "substituted alkyl," as used herein, refers to an "alkyl" group substituted by independent replacement of one or more (e.g., 1, 2, or 3) of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-C_1-C_6-alkyl, OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-(C_1-C_6-alkyl), CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-C_1-C_6 alkyl, SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-C_1-C_6-alkyl, SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-

cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2,$CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "haloalkyl," as used herein, refers to an acyclic, straight or branched chain alkyl substituent having one or more hydrogen substituted for a halogen selected from bromo, chloro, fluoro, or iodo.

The term "thioalkyl," as used herein, refers to an acyclic, stright or branched chain alkyl substituent containing a thiol group, such as, for example and not limitation, thiopropyl.

The term "alkoxy," as used herein, refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy and n-hexoxy.

The term "alkenyl," as used herein, denotes a monovalent group derived by the removal of a single hydrogen atom from a hydrocarbon moiety having at least one carbon-carbon double bond. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like.

The term "substituted alkenyl," as used herein, refers to an "alkenyl" group substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-(C_1-C_6-alkyl), OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_1-C_6-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl,$OCONH_2$, OCONH-C_1-C_6-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C_1-C_6-alkyl,NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12}

cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "alkynyl," as used herein, denotes a monovalent group derived by the removal of a single hydrogen atom from a hydrocarbon moiety having at least one carbon-carbon triple bond. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1 -propynyl, 1 -butynyl, and the like.

The term "substituted alkynyl," as used herein, refers to an "alkynyl" group substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-(C_1-C_6-alkyl), OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-(C_1-C_6-alkyl), CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetra hyd rona phthyl, indanyl, idenyl and the like.

The term "substituted aryl," as used herein, refers to an aryl group, as defined herein, substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-(C_1-C_6-alkyl), OCH_2-(C_3-

C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-(C_1-C_6-alkyl), CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "arylalkyl," as used herein, refers to a Cl-C3 alkyl or Cl-C6 alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "substituted arylalkyl," as used herein, refers to an arylalkyl group, as previously defined, substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-C_1-C_6-alkyl, OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_1-C_6-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino,

arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "cycloalkyl" denotes a monovalent group derived by the removal of a single hydrogen atom from a monocyclic or bicyclic saturated carbocyclic ring compound. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The term "substituted cycloalkyl," as used herein, refers to a cycloalkyl group as defined herein, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-(C_1-C_6-alkyl), OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-(C_1-C_6-alkyl), CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6-alkyl), OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO2-heteroaryl, OCONH2, OCONH-Cl-C6-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The terms "heterocyclo" and "heterocyclic" as used herein, refer to a monovalent substituent derived by removal of a hydrogen from a three to seven-membered saturated or unsaturated (including aromatic) cycle having 1 to 4 non-carbon ring atoms selected from the heteroatoms consisting of N, O, and S. Examples of suitable heterocycles include but are not limited to tetrahydrofuran, thiophene, diazepine, isoxazole, piperidine, dioxane, morpholine, and pyrimidine. The term also includes a heterocycle as defined herein fused to one or more other cycles whether hetero or carbocyclic. One example is thiazolo[4,5-b]-pyridine. Although the terms "heterocycloalkyl," "aliphatic heteromonocyclic ring system," "aliphatic heterobicyclic ring

system," "aliphatic heterotricyclic ring system," "heteroaryl," "aromatic heteromonocyclic ring system," "aromatic heterobicyclic ring system," "aromatic heterotricyclic ring system," "heteroarylalkyl," are covered generally by the term "heterocycle," their specific meanings are set forth in further detail below.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic 5-, 6- or 7-membered ring or a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to a benzene ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetra hydrofuryl.

The term "substituted heterocycloalkyl," as used herein, refers to a heterocycloalkyl group, as previously defined, substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-C_1-C_6-alkyl, OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_1-C_6-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C_1-C_6-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

As used herein, the term "aliphatic heteromonocyclic ring system" is intended to mean a ring system containing a non-aromatic ring that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. The term "aliphatic heterobicyclic ring system" is intended to mean a ring system containing a two fused rings, at least one of which is a non-aromatic ring that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. The term "aliphatic heterotricyclic ring system" is intended to mean a ring system containing three fused rings, at least one of which is a non-aromatic ring that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. As will be appreciated, the aliphatic heterocyclic ring systems can possess any degree of saturation (i.e., double or triple bonds) provided that none of the heteroatom-containing constituent rings are aromatic. Thus, structures such as indoline, which contains a non-aromatic heterocyclic ring (i.e., a pyrroline ring) fused to an aromatic carbocyclic ring (specifically, a phenyl ring), and phthalimide, are examples of an "aliphatic heterobicyclic ring systems."

As used herein, the term "aromatic heteromonocyclic ring system" is intended to mean an aromatic ring that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. The term "aromatic heterobicyclic ring system" is intended to mean an aromatic ring system containing two fused rings that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. The term "aromatic heterotricyclic ring system" is intended to mean an aromatic ring system containing three fused rings that includes at least one ring hetero (i.e., non-carbon) atom selected from O, N and S. Substituent atoms of the aromatic heterocyclic ring systems can, together with additional atoms, form further fused ring structures that are not aromatic. Thus, 5,6, 7,8 tetrahydroisoquinoline is an example of an aromatic heterobicyclic ring system, whereas 1,2,3,4 tetrahydroisoquinoline is an example of an aliphatic heterobicyclic ring system.

The term "heteroaryl," as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which at least one ring atom is selected from S, O and Nand the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridinyl, pyrazinyl,

pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

The term "substituted heteroaryl," as used herein, refers to a heteroaryl group as defined herein, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-C_1-C_6-alkyl, OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-(C_1-C_6-alkyl), CONH-aryl, CONH-heteroaryl, OC(O)-(C_1-C_6)-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C1-C6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

The term "heteroarylalkyl," as used herein, refers to a C_1-C_3 alkyl or C_1-C_6 alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "substituted heteroarylalkyl," as used herein, refers to a heteroarylalkyl group, as previously defined, substituted by independent replacement of one or more of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO_2, CN, C_1-C_6-alkyl-OH, C(O)-C_1-C_6-alkyl, OCH_2-(C_3-C_{12}-cycloalkyl), C(O)-aryl, C(O)-heteroaryl, CO_2-alkyl, CO_2-aryl, CO_2-heteroaryl, $CONH_2$, CONH-C_1-C_6-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C_1-C_6-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO_2-alkyl, OCO_2-aryl, OCO_2-heteroaryl, $OCONH_2$, OCONH-(C_1-C_6-alkyl), OCONH-aryl, OCONH-heteroaryl, NHC(O)-(C_1-C_6-alkyl), NHC(O)-aryl, NHC(O)-heteroaryl, $NHCO_2$-alkyl, $NHCO_2$-aryl, $NHCO_2$-heteroaryl, $NHCONH_2$, NHCONH-(C_1-C_6-alkyl), NHCONH-aryl, NHCONH-heteroaryl, SO_2-(C_1-C_6-alkyl), SO_2-aryl, SO_2-heteroaryl, SO_2NH_2, SO_2NH-(C_1-C_6-alkyl), SO_2NH-aryl, SO_2NH-

heteroaryl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, CF_3, CH_2CF_3, $CHC1_2$, CH_2NH_2, $CH_2SO_2CH_3H$, C_1-C_6 alkyl, halo alkyl, C_3-C_{12} cycloalkyl, substituted C_3-C_{12} cycloalkyl, aryl, substituted aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C_1-C_6-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C_1-C_3-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C_1-C_6-alkyl-thio, or methylthiomethyl.

Substituent groups substituted on any group (e.g., alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, heterocyclic) delineated herein also include any of –F, –Cl, –Br, –I, –OH, protected hydroxy, aliphatic ethers, aromatic ethers, oxo, $-NO_2$, –CN, $-C_1$-C_{12}-alkyl optionally substituted with halogen (such as perhaloalkyls), C_2-C_{12}-alkenyl optionally substituted with halogen, $-C_2$-C_{12}-alkynyl optionally substituted with halogen, $-NH_2$, protected amino, –NH -C_1-C_{12}-alkyl, –NH -C_2-C_{12}-alkenyl, –NH -C_2-C_{12}-alkynyl, –NH -C_3-C_{12}-cycloalkyl, –NH -aryl, –NH -heteroaryl, –NH -heterocycloalkyl, –dialkylamino, –diarylamino, –diheteroarylamino, –O-C_1-C_{12}-alkyl, –O-C_2-C_{12}-alkenyl, –O-C_2-C_{12}-alkynyl, –O-C_3-C_{12}-cycloalkyl, –O-aryl, –O-heteroaryl, –O-heterocycloalkyl, –C(O)- C_1-C_{12}-alkyl, –C(O)- C_2-C_{12}-alkenyl, –C(O)- C_2-C_{12}-alkynyl, –C(O)-C_3-C_{12}-cycloalkyl, –C(O)-aryl, –C(O)-heteroaryl, –C(O)-heterocycloalkyl, $-CONH_2$, –CONH- C_1-C_{12}-alkyl, –CONH- C_2-C_{12}-alkenyl, –CONH- C_2-C_{12}-alkynyl, –CONH-C_3-C_{12}-cycloalkyl, –CONH-aryl, –CONH-heteroaryl, –CONH-heterocycloalkyl, $-CO_2$- C_1-C_{12}-alkyl, $-CO_2$-C_2-C_{12}-alkenyl, $-CO_2$- C_2-C_{12}-alkynyl, $-CO_2$-C_3-C_{12}-cycloalkyl, $-CO_2$-aryl, $-CO_2$-heteroaryl, $-CO_2$-heterocycloalkyl, $-OCO_2$- C_1-C_{12}-alkyl, $-OCO_2$- C_2-C_{12}-alkenyl, $-OCO_2$- C_2-C_{12}-alkynyl, $-OCO_2$-C_3-C_{12}-cycloalkyl, $-OCO_2$-aryl, $-OCO_2$-heteroaryl, $-OCO_2$-heterocycloalkyl, $-OCONH_2$, –OCONH- C_1-C_{12}-alkyl, –OCONH- C_2-C_{12}-alkenyl, –OCONH- C_2-C_{12}-alkynyl, –OCONH- C_3-C_{12}-cycloalkyl, –OCONH- aryl, –OCONH-heteroaryl, –OCONH- heterocycloalkyl, –NHC(O)- C_1-C_{12}-alkyl, –NHC(O)-C_2-C_{12}-alkenyl, –NHC(O)-C_2-C_{12}-alkynyl, –NHC(O)-C_3-C_{12}-cycloalkyl, –NHC(O)-aryl, –NHC(O)-heteroaryl, –NHC(O)-heterocycloalkyl, $-NHCO_2$- C_1-C_{12}-alkyl, $-NHCO_2$- C_2-C_{12}-alkenyl, $-NHCO_2$- C_2-C_{12}-alkynyl, $-NHCO_2$- C_3-C_{12}-cycloalkyl, $-NHCO_2$- aryl, $-NHCO_2$-heteroaryl, $-NHCO_2$- heterocycloalkyl, $-NHC(O)NH_2$, NHC(O)NH- C_1-C_{12}-alkyl, –NHC(O)NH-C_2-C_{12}-alkenyl, –NHC(O)NH-C_2-C_{12}-alkynyl, –NHC(O)NH-C_3-C_{12}-

cycloalkyl, –NHC(O)NH-aryl, –NHC(O)NH-heteroaryl, –NHC(O)NH-heterocycloalkyl, NHC(S)NH_2, NHC(S)NH- C_1-C_{12}-alkyl, –NHC(S)NH-C_2-C_{12}-alkenyl, –NHC(S)NH-C_2-C_{12}-alkynyl, –NHC(S)NH-C_3-C_{12}-cycloalkyl, –NHC(S)NH-aryl, –NHC(S)NH-heteroaryl, –NHC(S)NH-heterocycloalkyl, –NHC(NH)NH_2, NHC(NH)NH- C_1-C_{12}-alkyl, –NHC(NH)NH-C_2-C_{12}-alkenyl, –NHC(NH)NH-C_2-C_{12}-alkynyl, –NHC(NH)NH-C_3-C_{12}-cycloalkyl, –NHC(NH)NH-aryl, –NHC(NH)NH-heteroaryl, –NHC(NH)NH-heterocycloalkyl, NHC(NH)-C_1-C_{12}-alkyl, –NHC(NH)-C_2-C_{12}-alkenyl, –NHC(NH)-C_2-C_{12}-alkynyl, –NHC(NH)-C_3-C_{12}-cycloalkyl, –NHC(NH)-aryl, –NHC(NH)-heteroaryl, –NHC(NH)-heterocycloalkyl, –C(NH)NH-C_1-C_{12}-alkyl, –C(NH)NH-C_2-C_{12}-alkenyl, –C(NH)NH-C_2-C_{12}-alkynyl, –C(NH)NH-C_3-C_{12}-cycloalkyl, –C(NH)NH-aryl, –C(NH)NH-heteroaryl, –C(NH)NH-heterocycloalkyl, –S(O)-C_1-C_{12}-alkyl, – S(O)-C_2-C_{12}-alkenyl, – S(O)-C_2-C_{12}-alkynyl, – S(O)-C_3-C_{12}-cycloalkyl, – S(O)-aryl, – S(O)-heteroaryl, – S(O)-heterocycloalkyl –SO_2NH_2, –SO_2NH- C_1-C_{12}-alkyl, –SO_2NH- C_2-C_{12}-alkenyl, –SO_2NH-C_2-C_{12}-alkynyl, –SO_2NH- C_3-C_{12}-cycloalkyl, –SO_2NH- aryl, –SO_2NH- heteroaryl, –SO_2NH- heterocycloalkyl, –$NHSO_2$-C_1-C_{12}-alkyl, –$NHSO_2$-C_2-C_{12}-alkenyl, – $NHSO_2$-C_2-C_{12}-alkynyl, –$NHSO_2$-C_3-C_{12}-cycloalkyl, –$NHSO_2$-aryl, –$NHSO_2$-heteroaryl, –$NHSO_2$-heterocycloalkyl, –CH_2NH_2, –$CH_2SO_2CH_3$, –aryl, –arylalkyl, –heteroaryl, –heteroarylalkyl, –heterocycloalkyl, –C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, –methoxymethoxy, –methoxyethoxy, –SH, –S-C_1-C_{12}-alkyl, –S-C_2-C_{12}-alkenyl, –S-C_2-C_{12}-alkynyl, –S-C_3-C_{12}-cycloalkyl, –S-aryl, –S-heteroaryl, –S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls and the like can be further substituted.

The term "alkylamino," as used herein, refers to a group having the structure -NH(C_1-C_{12} alkyl) where C_1-C_{12} alkyl is as previously defined. The term "dialkylamino" refers to a group having the structure -N(C_1-C_{12} alkyl)$_2$ where C_1-C_{12} alkyl is as previously defined. Examples of dialkylamino are, but not limited to, N,N-dimethylamino, N,N-diethylamino, N,N-methylethylamino, piperidino, and the like.

The term "diarylamino" refers to a group having the structure -N(aryl)$_2$ or -N(substituted aryl)$_2$ where substituted aryl is as previously defined. Examples of

diarylamino are, but not limited to, N,N- diphenylamino, N,N-dinapthylamino, N,N-di(toluenyl)amino, and the like.

The term "diheteroarylamino" refers to a group having the structure -N(heteroaryl)$_2$ or -N(substituted heteroaryl)$_2$, where heteroaryl and substituted heteroaryl is as previously defined. Examples of diheteroarylamino are, but not limited to, N,N- difuranylamino, N,N-dithiazolidinylamino, N,N-di(imidazole)amino, and the like.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl- 3 -butenyl, allyl, benzyl, para-methoxybenzyldiphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-triehloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxyl protecting groups for the present invention are acetyl (Ac or -C(O)CH_3), benzoyl (Bn or -C(O)C_6H_5), and trimethylsilyl (TMS or-Si$(CH_3)_3$).

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "nitrogen (or amino) protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a nitrogen group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the nitrogen

protecting group as described herein may be selectively removed. Nitrogen protecting groups as known in the are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of nitrogen protecting groups include, but are not limited to, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

The term "nucleophilic heterocyclic compound" refers to a heterocyclic group in a nucleophilic form (e.g., metal salt form, protonated form) such that it is capable of reacting with another molecule resulting in a covalent bond between the two molecules (e.g., a nucleophile in a nucleophilic displacement reaction). Examples of such nucleophilic heterocyclic compounds are known in the art and delineated herein.

The term "leaving group: refers to a moiety that can be detached from a molecule during a reaction, especially nucleophilic displacement reactions. Examples of leaving groups include, for example, halides, mesyl groups, tosyl groups, alkoxides, hydroxides, and protonated forms thereof. Examples of such leaving groups are known in the art and delineated herein.

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further

discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protogenic organic solvent," as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts,

Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The term "subject" as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The term "subject" as used herein refers to a mammal. Preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs and the like.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate,

ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_1-C_6 sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, but are not limited to, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs," as used herein, refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable risk/reward ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, *Prodrugs as Novel delivery*

Systems, Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design* (American Pharmaceutical Association and Pergamon Press, 1987), both of which are incorporated by reference herein.

The term "effective amount" or "therapeutically effective amount," as used herein, means an amount which is capable of inhibiting the HCV NS3 serine protease, therefore interfering with the production of the viral polyprotein essential for viral replication. The HCV serine protease inhibition contemplated by the present method includes both therapeutic and prophylactic treatment, as appropriate for the subject in need of such treatment. Methods of treatment, dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of the present invention may be combined with a pharmaceutically acceptable excipient for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection. Alternatively, the compounds of the present invention may be used in vaccines and methods for protecting individuals against HCV viral infection over an extended period of time. The compounds may be employed in a manner consistent with the conventional utilization of protease inhibitors in vaccines. For example, a compound of the present invention may be combined with pharmaceutically acceptable excipients conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against HCV viral infection. As such, the protease inhibitors of the present invention can be administered as agents for treating or preventing HCV viral infection in a subject.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds described herein contain two or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- , or as (D)- or (L)- for

amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers Racernates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as trans may be cis, trans, or a mixture of the two in any proportion.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some Examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil ; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as

well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents, commonly used in the art such as, for example, water or other solvents, solubilizing agents and 30 emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethy1formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and

can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention. The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Antiviral Activity

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject, such as a human or lower mammal, by administering to the subject an effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, means a sufficient amount of the compound so as to decrease the viral load in a

subject, thus decreasing said subject's chronic HCV symptoms. As well understood in the medical arts an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific anti-HCV virally effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

ACN for acetonitrile;

BME for 2-mercaptoethanol;

BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;

COD for cyclooctadiene;

DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminohexyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;

DAST for diethylaminosulfur trifluoride;

DCM for dichloromethane;

DIAD for diisopropyl azodicarboxylate;

DIBAL-H for diisobutylaluminum hydride;

DIEA for diisopropyl ethylamine;

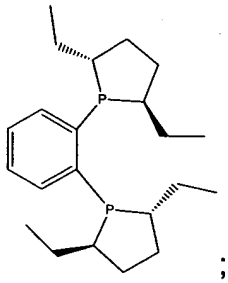
DMAP for N,N-dimethylaminopyridine;

DME for ethylene glycol dimethyl ether;

DMEM for Dulbecco's Modified Eagles Media;

DMF for N,N-dimethyl formamide;

DMSO for dimethylsulfoxide;

DUPHOS for  ;

EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;

EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

EtOAc for ethyl acetate;

HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N' – tetramethyluronium hexafluorophosphate;

HMBA is 4-Hydroxymethylbenzoic acid AM resin;

Hoveyda's Cat. for Dichloro(o-isopropoxyphenylmethylene) (tricyclohexylphosphine)ruthenium(II);

KHMDS is potassium bis(trimethylsilyl) amide;

Ms for mesyl;

NMM for N-4-methylmorpholine

Ph for phenyl;

PuPHOS

PyBrOP for Bromo-tri-pyrolidino-phosphonium hexafluorophosphate;

RCM for ring-closing metathesis;

RT for room temperature;

RT-PCR for reverse transcription-polymerase chain reaction;

tBOC or Boc for tert-butyloxy carbonyl.

TEA for triethyl amine;

TFA for trifluoroacetic acid;

THF for tetrahydrofuran;

TLC for thin layer chromatography;

TPP or PPh3 for triphenylphosphine; and

Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene.

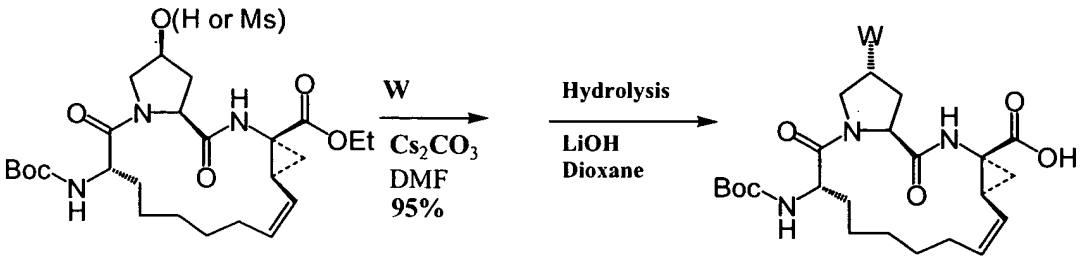
Certain chemical structures herein having –NH or –OH groups appear without those hydrogen atoms attached to oxygen or nitrogen atoms depicted. Thus, where a nitrogen or oxygen atom in such structure appears to lack proper valency, the presence of those hydrogen atoms are implied.

SYNTHETIC METHODS

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared.

I. Replacement Method

Compounds of the present invention can be made via a replacement procedure described generally in the following scheme:

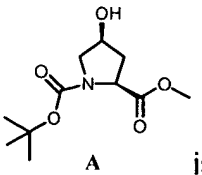


The hydroxyl proline or mesylated proline precursor may be used. This replacement method protocol is suitable for converting any hydroxy (or corresponding mesylate) proline compound or derivative starting compound to a heterocyclic substituted proline derivative. The subsequent synthetic methods set forth the various procedures and intermediate steps that may be used to prepare the compounds disclosed herein.

A. Synthesis Of Hydroxyl Proline Cyclic Peptide Precursors

A cyclic peptide precursor may be used to synthesize the compounds of the invention. In some embodiments, a mesylated version of the cyclic precursor may be used.

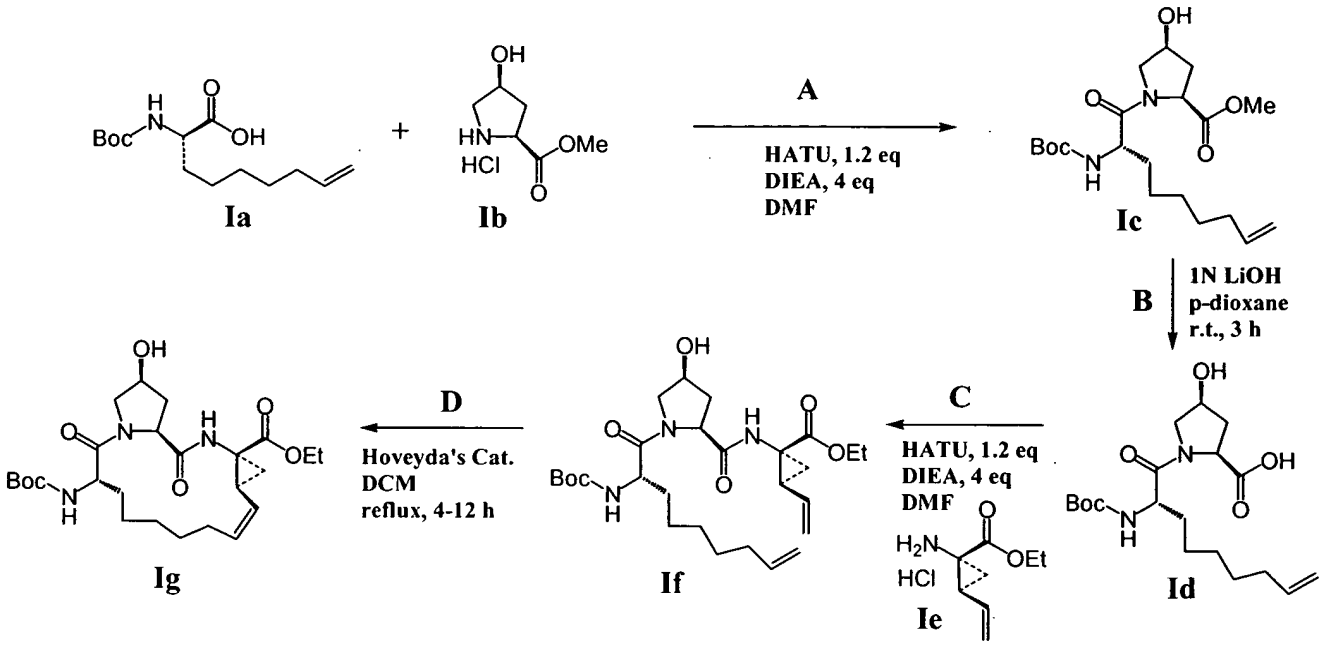
In some embodiments, commercially available Boc-hydroxyproline **A**



A is treated with HCl in dioxane to yield starting material **Ib**.

Synthesis of Cyclic peptide precursor

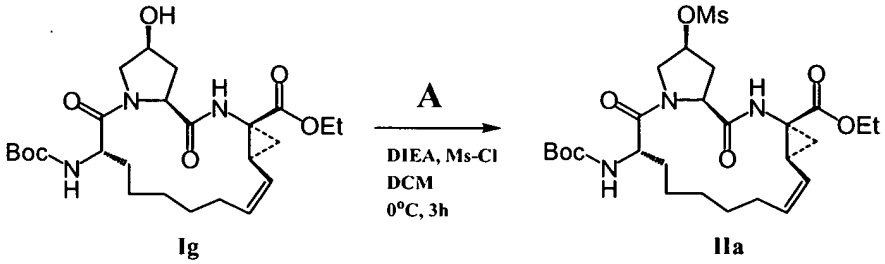
Scheme 1



The cyclic peptide precursor Ig was synthesized from Boc-L-2-amino-8-nonenoic acid **Ia** and *cis*-L-hydroxyproline methyl ester **Ib** via steps A-D set forth generally in Scheme 1. For further details of the synthetic methods employed to produce the cyclic peptide precursor Ig, see U.S. Patent No. 6,608,027, which is herein incorporated by reference in its entirety.

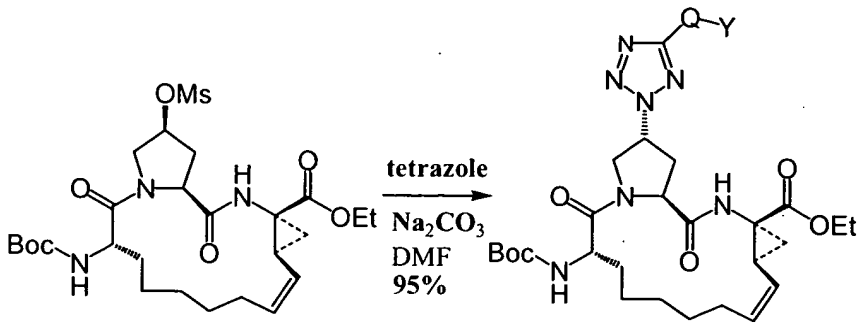
Synthesis of mesylate of macrocyclic peptide precursor

Scheme 2



The cyclic precursor mesylate was synthesized by forming the mesylate upon the hydroxyl of the hydroxyl proline residue of the cyclic peptide precursor via the synthetic route generally described above in Scheme 2.

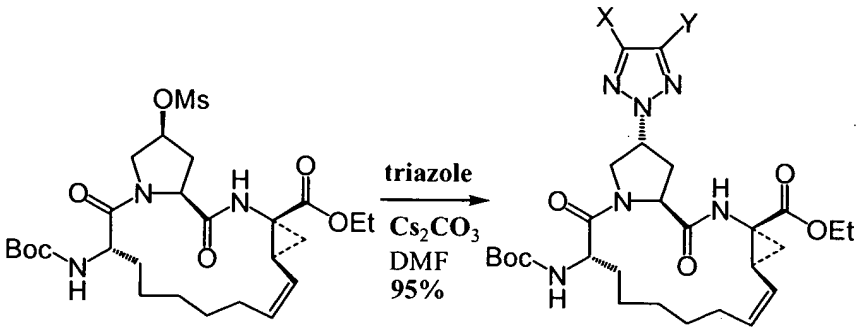
Scheme 3



IIa III

The compounds of the present invention are made via the replacement of the mesylate of the macrocyclic peptide mesylate **IIa** with a 5-substituted-2*H*-tetrazole, Exemplary syntheses of such tetrazoloes as described in Scheme 5, below, via the synthetic route described generally in Scheme 3.

Scheme 4



IIa IVa

The compounds of the present invention are made via the replacement of the mesylate of the macrocyclic peptide mesylate **IIa** with a 4,5-substituted-1H-triazole via the synthetic route described generally in Scheme 4. Exemplary syntheses of such triazoles are described in scheme 6, below.

B. Synthesis of substitutes for W

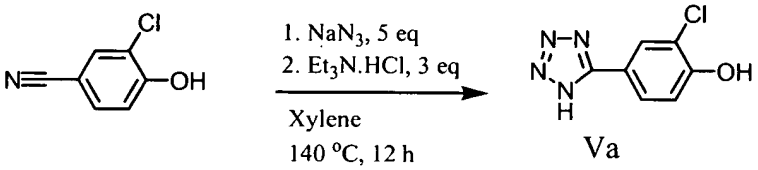
W may be any of the substitutents described previously herein. Synthesis of these various substituents is within the skill of those of ordinary skill in the art. Some exemplary syntheses are presented herein by way of example and not of limitation.

Other substituents are either commercially available or readily synthesized by those of ordinary skill in the art.

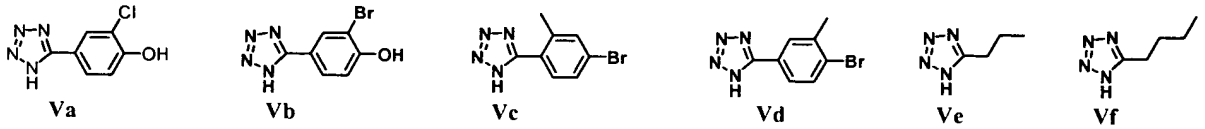
Synthesis of tetrazoles

Structurally diverse tetrazoles Va-Vq were synthesized from commercially available nitrile compounds as described in Scheme 5 below:

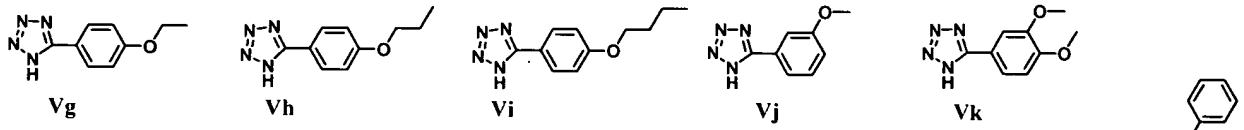
Scheme 5



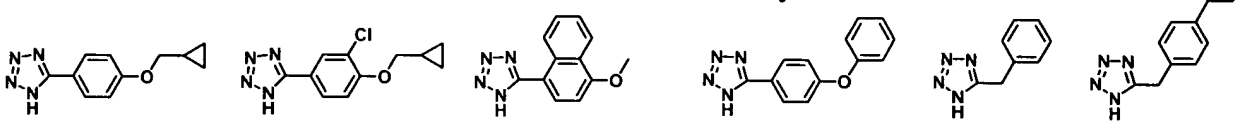
Va



Va Vb Vc Vd Ve Vf



Vg Vh Vi Vj Vk

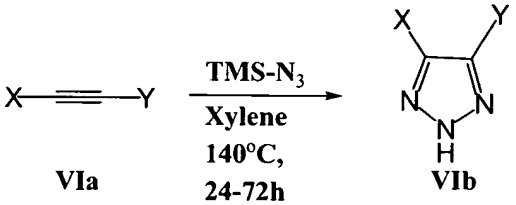


Vl Vm Vn Vo Vp Vq

One skilled in the art will recognize that several 5-substituted tetrazole compounds may be produced in this manner with any nitrile-containing compound suitable for the reaction conditions set forth above.

Synthesis of triazoles

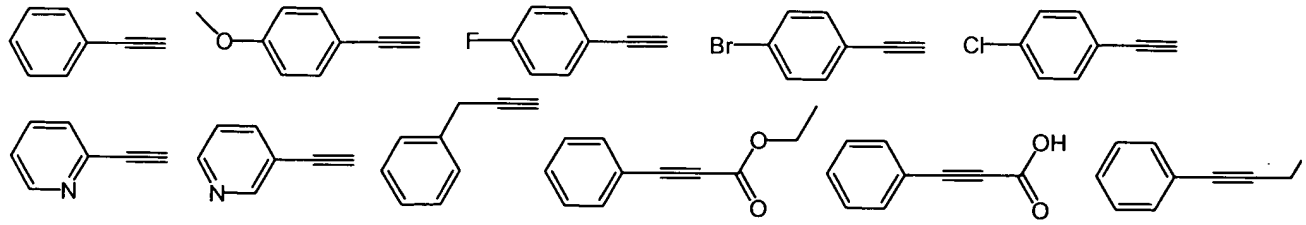
Scheme 6



VIa VIb

Triazoles of the present invention are prepared by reacting alkyne compound VIa, which is commercially available or made from procedures elucidated *infra*, and trimethylsilyl azide via the synthetic route described generally in Scheme 6.

Commercially available alkynes suitable for triazole formation include, but are not limited to:

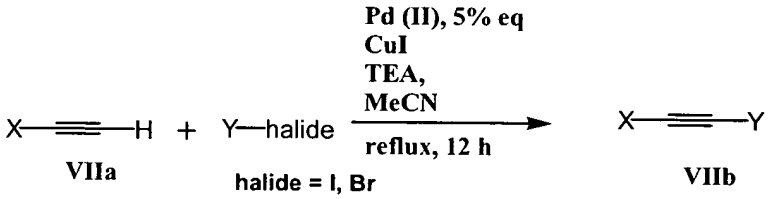


Synthesis of alkynes

Alkynes useful in the synthesis of triazoles may be made by any appropriate method. Below are some exemplary syntheses.

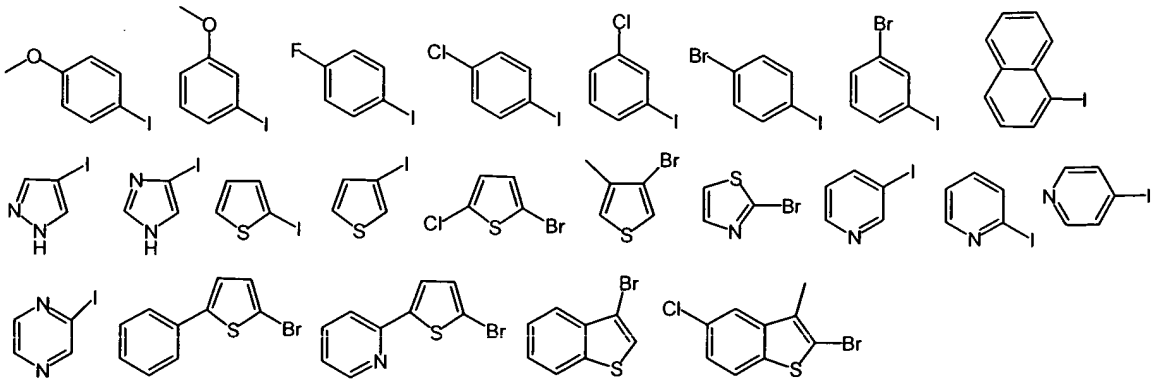
Sonogashira reaction

Scheme 7

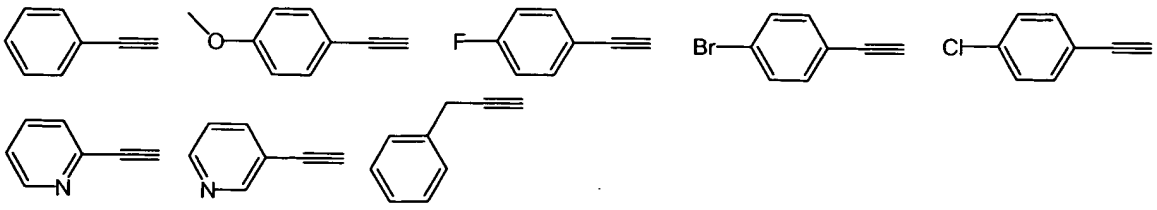


Alkynes used in the present invention can be made by the Sonogashira reaction with primary alkyne compound VIIa, an aryl halide (Y–halide), and triethylamine in acetonitrile with $PdCl_2(PPh_3)_2$ and CuI via the synthetic route described generally in Scheme 7.

Commercially–available aryl halides suitable for the Sonogashira reaction include, but are not limited to:

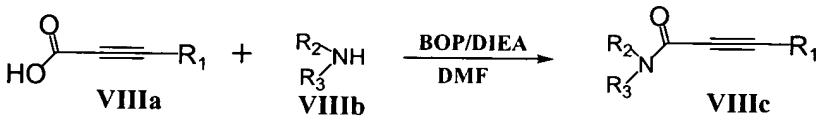


Commercially-available primary alkynes suitable for the Sonogashira reaction include, but are not limited to:



Synthesis of alkynyl amides

Scheme 8



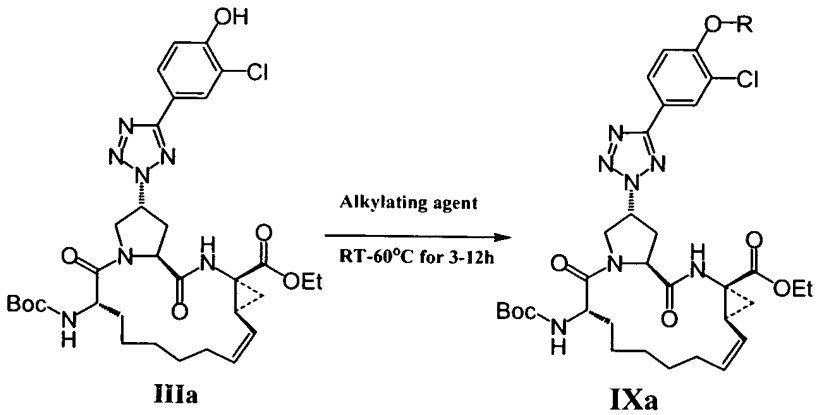
Additional alkynes used in the present invention can be made by reacting alkynyl acid Va, BOP, and DIEA in DMF with amine VIIIb via the synthetic route described generally in Scheme 8.

Post-Replacement Modification

The resultant macrocyclcic compound may be modified after W is attached. Some exemplary modifications follow.

1. Synthesis of Phenolic esters

Scheme 9



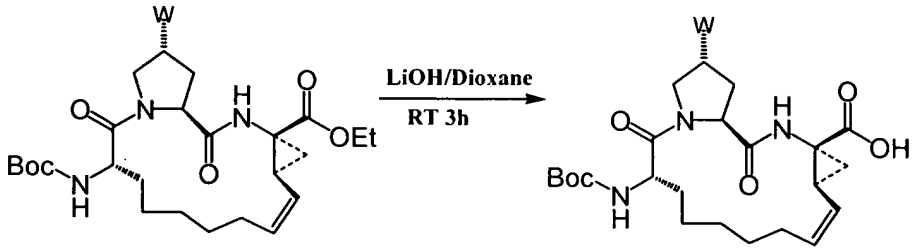
IIIa IXa

R = methyl, ethyl, allyl, 2-hydroxyethyl, isopropyl, methiomethyl

The post-replacement modification of macrocyclic compound IIIa to obtain various phenolic esters was performed by the synthetic route described generally in Scheme 9.

2. Hydrolysis of macrocyclic peptide ethyl ester-

Scheme 10

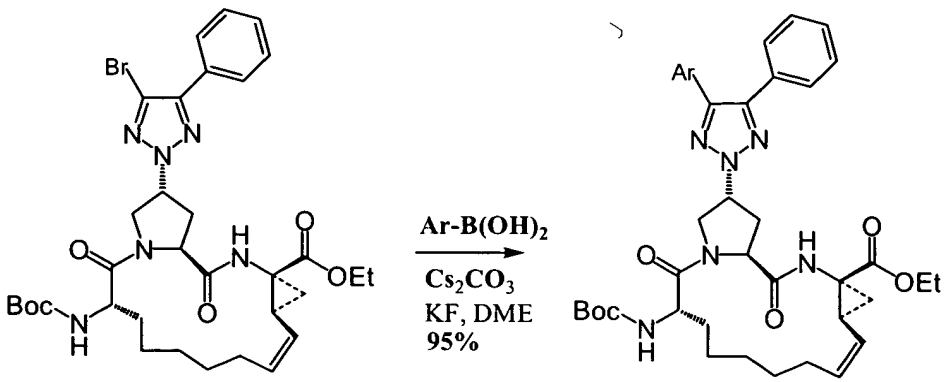


IVa IVa

The hydrolysis of macrocyclic peptide ethyl esters of the present invention is performed by dissolving macrocyclic peptide ethyl ester IV in dioxane and adding 1M LiOH via the synthetic route described generally in Scheme 10.

3. Using Suzuki coupling to generate more bi-aryl compounds

Scheme 11



XIa XIb

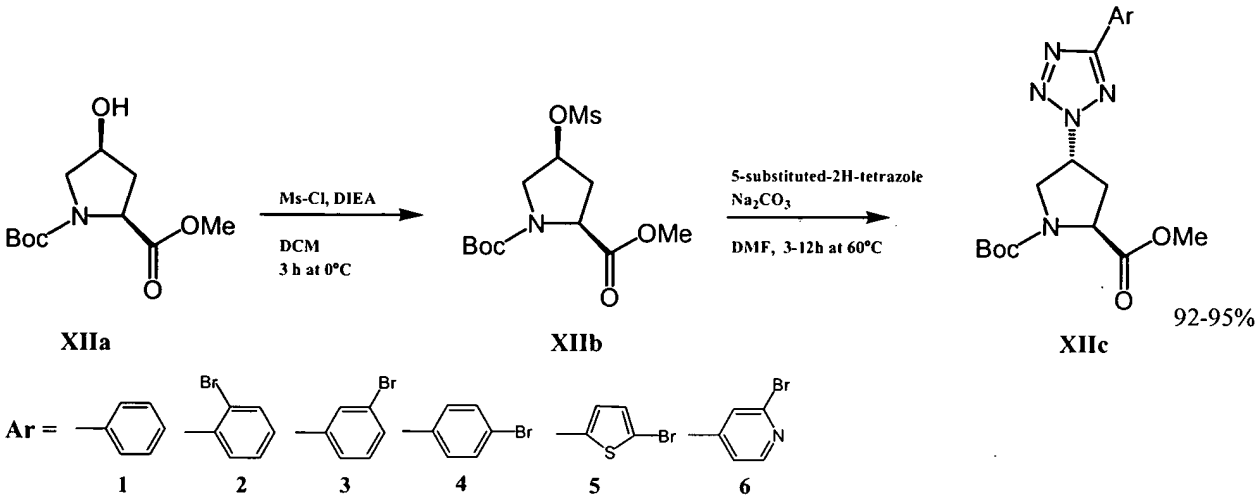
Compounds of the present invention may be further diversified by performing a Suzuki coupling adding to bromo-substituted triazole macrocyclic ethyl ester (see *infra* Example 26 for preparation) DME an aromatic boric acid, cesium carbonate and KF via the synthetic route described generally in Scheme 11.

II. Stepwise Synthesis

Compounds of the invention may also be prepared though a stepwise synthesis rather than a replacement mechanism. Below is an exemplary synthesis where W is a tetrazole.

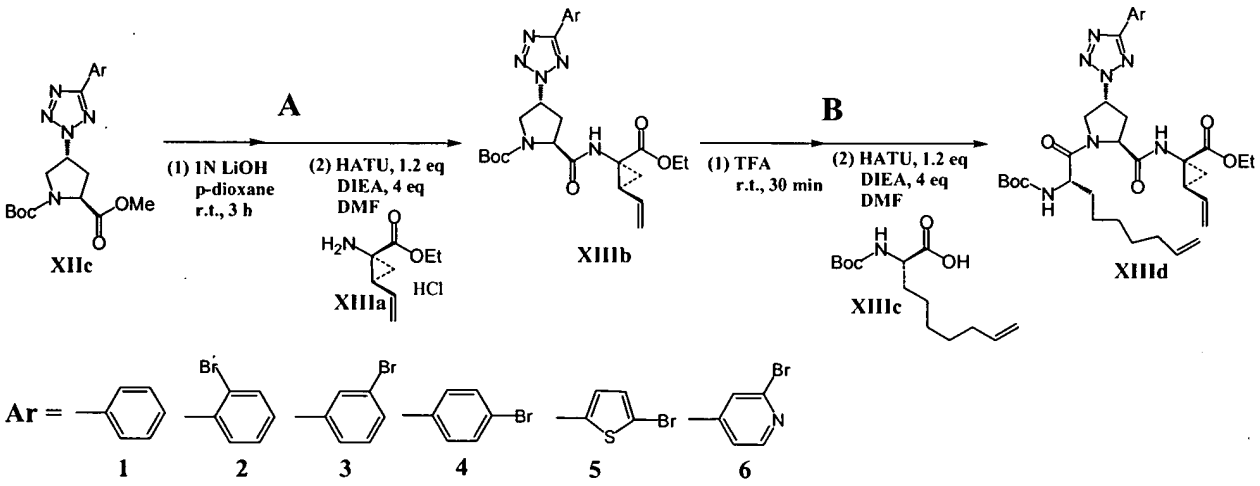
A. Synthesis of proline derivatives.

Scheme 12



B. Synthesis of linear tripeptides.

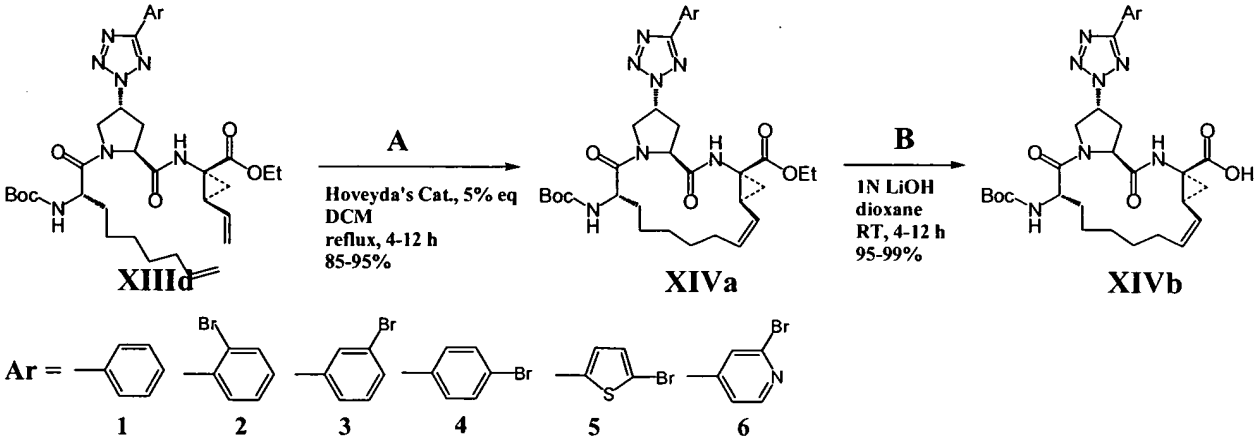
Scheme 13



The linear tri-peptide containing tetrazole-substituted proline derivatives XIIc were prepared via the synthetic route described generally in Scheme 12.

C. Synthesis of cyclic peptide via Ring-closing-Metathesis (RCM).

Scheme 14

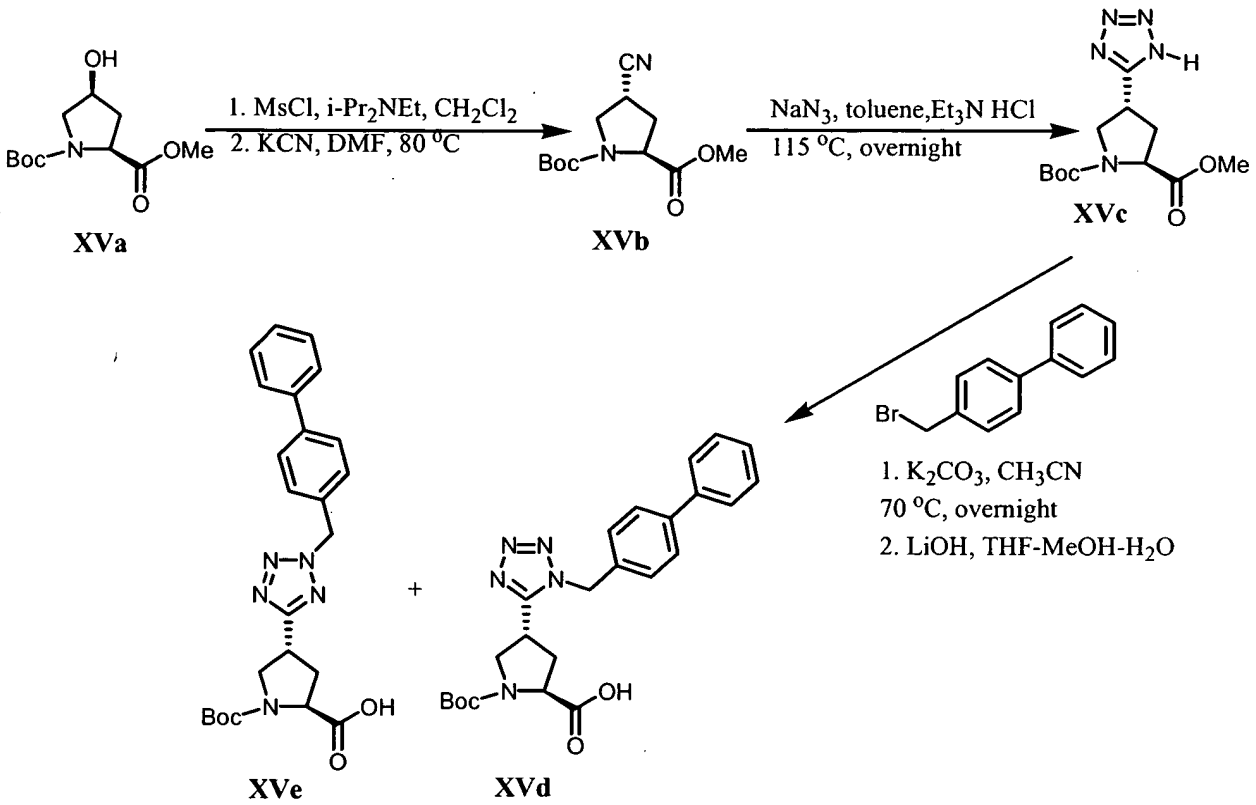


Formation of macrocyclic compound Xb was performed using linear tripeptide XIIId via the Ring-Closing Metathesis reaction described generally in Scheme 14.

D. Other derivatives

1. Tetrazole-substituted proline derivatives of the present invention were synthesized by the synthetic route described generally in Scheme 12.

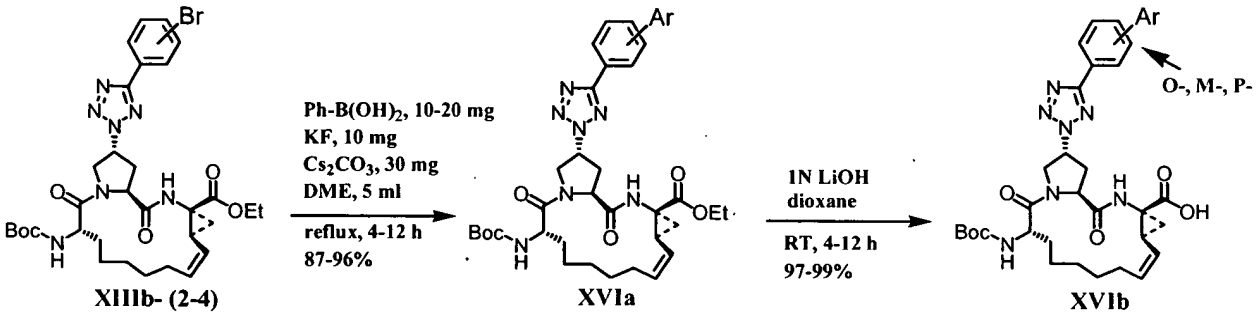
Scheme 15



Additional tetrazole-substituted proline derivatives of the present invention were synthesized by the synthetic route described generally in Scheme 15.

2. Suzuki coupling

Scheme 16



Further derivatives were prepared using the Suzuki Coupling reaction described generally in Scheme 16.

III. SOLID PHASE SYNTHESIS

Some compounds of the invention are amenable to synthesis by solid phase synthesis. For example, the triazole-substituted proline derivatives (P2) can be

synthesized and used in an on-resin assembly of a linear tripeptide chain. The resin-bound tripeptides, containing the triazole-substituted proline derivatives, undergo Ring-Closing-Metathesis (RCM) to furnish a cyclic tripeptide that is cleaved from the resin by hydrolysis affording the final product.

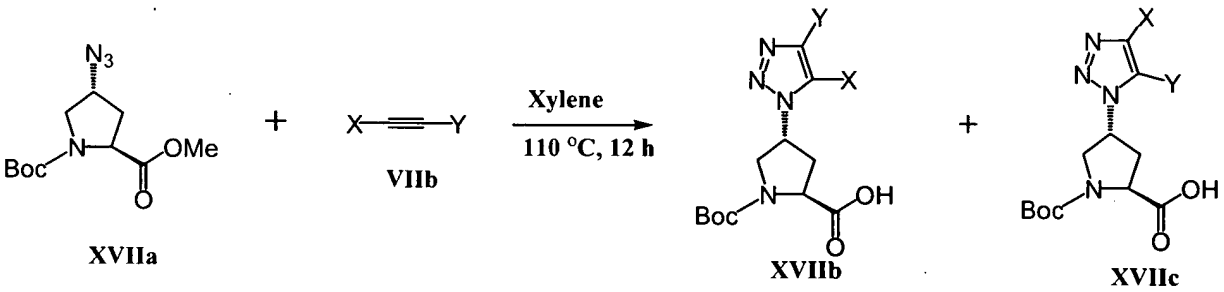
The following synthetic schemes set forth manners in which the triazole-substituted proline derivatives are made and the solid-phase synthesis of the compounds of the present invention.

A. Synthesis of proline derivatives

Two methods were employed to synthesize the triazole-substituted proline derivatives which are described generally by the following schemes:

1. Cyclo-addition method

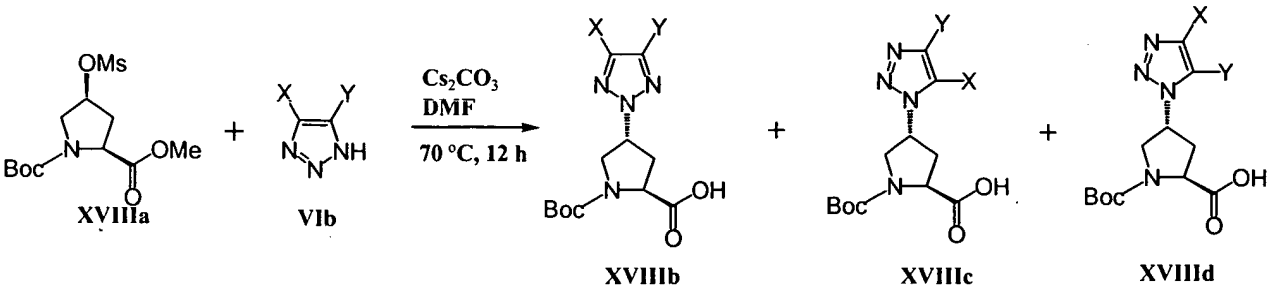
Scheme 17



The cyclo-addition method to create triazolyl proline derivatives involves the 3+2 cyclo-addition of azide proline derivative XVIIb and alkyne VIIb via the synthetic route described generally in Scheme 17. Exemplary syntheses of alkynes are described in Scheme 7 above.

2. Mesylate method

Scheme 18

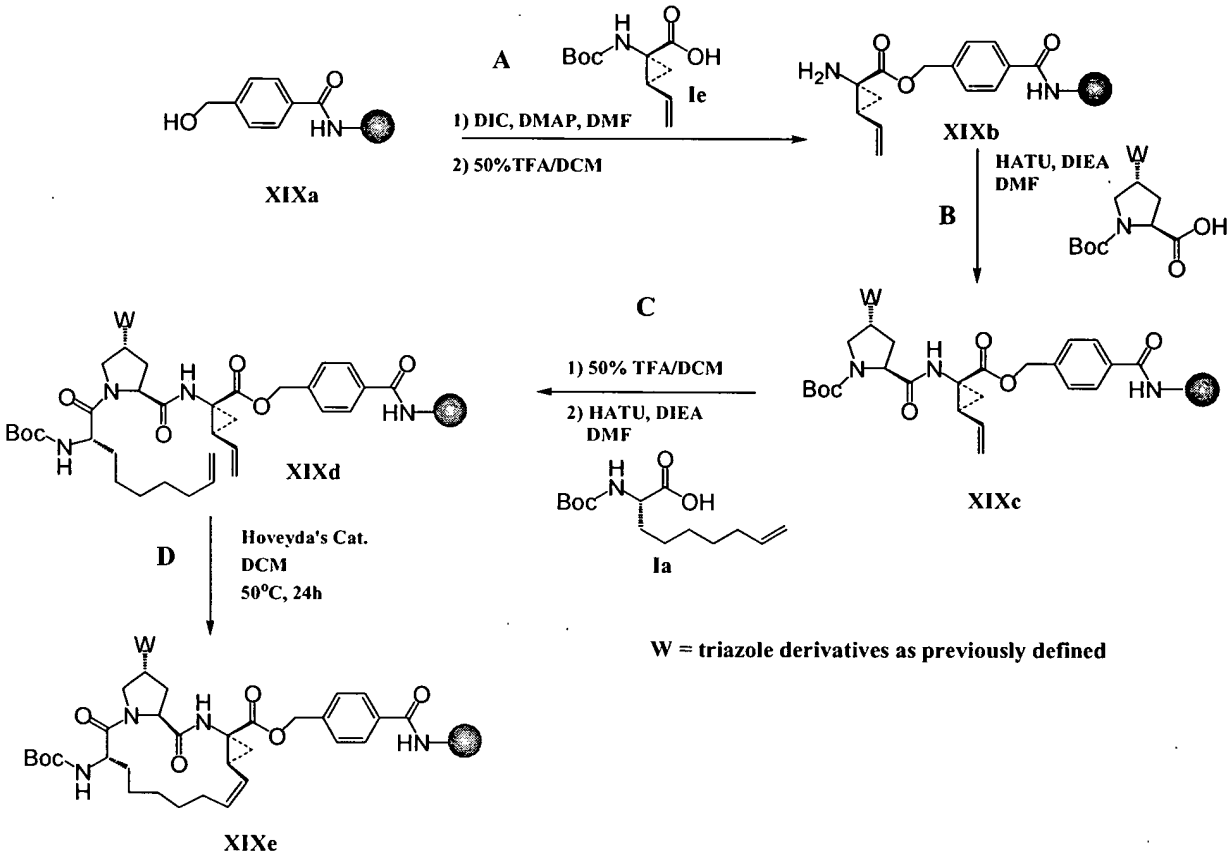


Additional proline derivatives were synthesized via the replacement of mesylate XVIIIa

with a 4,5-substituted-1H-triazole via the synthetic route described generally in Scheme 18.

B. On-resin assembly and on-resin RCM

Scheme 19



On resin assembly

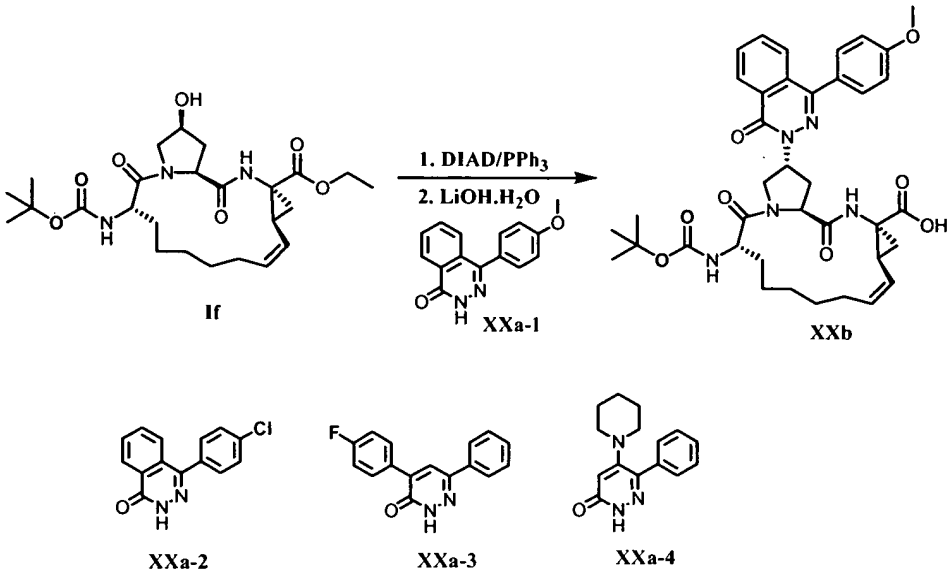
The on-resin assembly of linear peptide XIXd followed by the on-resin RCM to obtain resin-bound cyclic peptide precursor XIXe was performed via steps A-D described generally in Scheme 19.

IV. Other reactions

In some embodiments, the substituent W is well-suited to other types of reactions. For example, and not by limitation, when W is a pyridazinone, the following reaction schemes are used. These methods may be used for other substituents, but are discussed here in the context of pyridazinones.

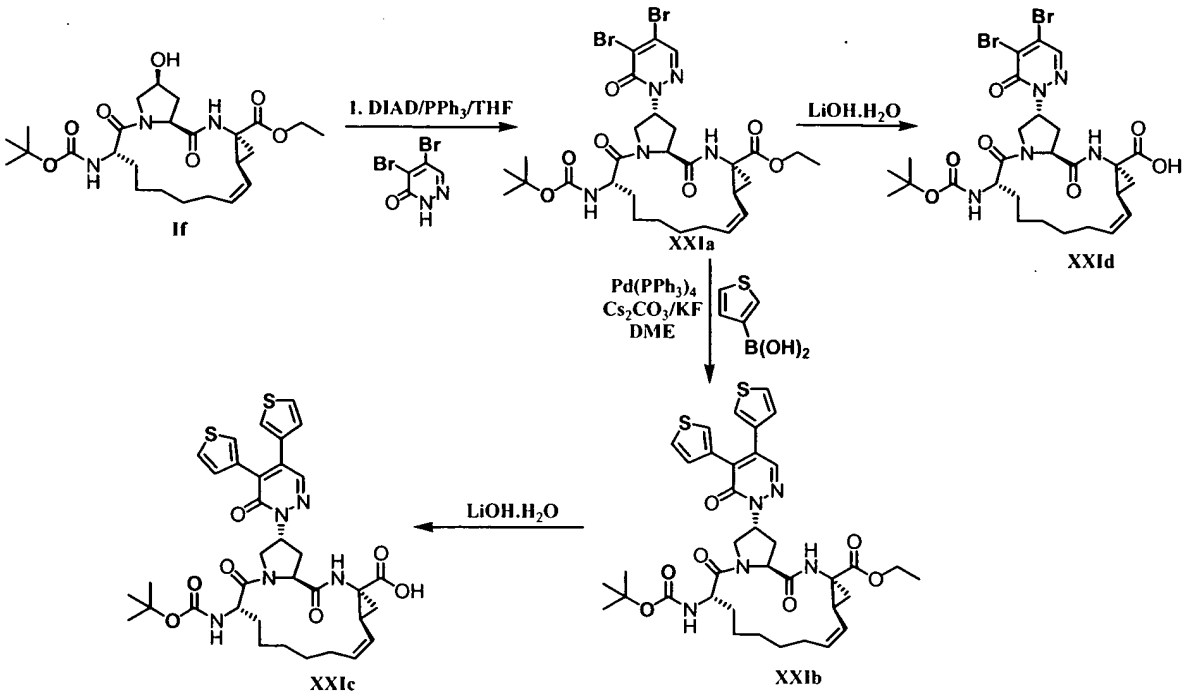
A. Condensation Reactions

Scheme 20



The simplest method, shown in Scheme 20, is to condense commercially available pyridazinones (XXa-1 – XXa-4) with key intermediate If by using Mitsunobu conditions followed by hydrolysis with LiOH. For further details on the Mitsunobu reaction see O. Mitsunobu, *Synthesis* 1981, 1-28; D. L. Hughes, *Org. React.* 29, 1-162 (1983); D. L. Hughes, *Organic Preparations and Procedures Int.* 28, 127-164 (1996); and J. A. Dodge, S. A. Jones, *Recent Res. Dev. Org. Chem.* 1, 273-283 (1997).

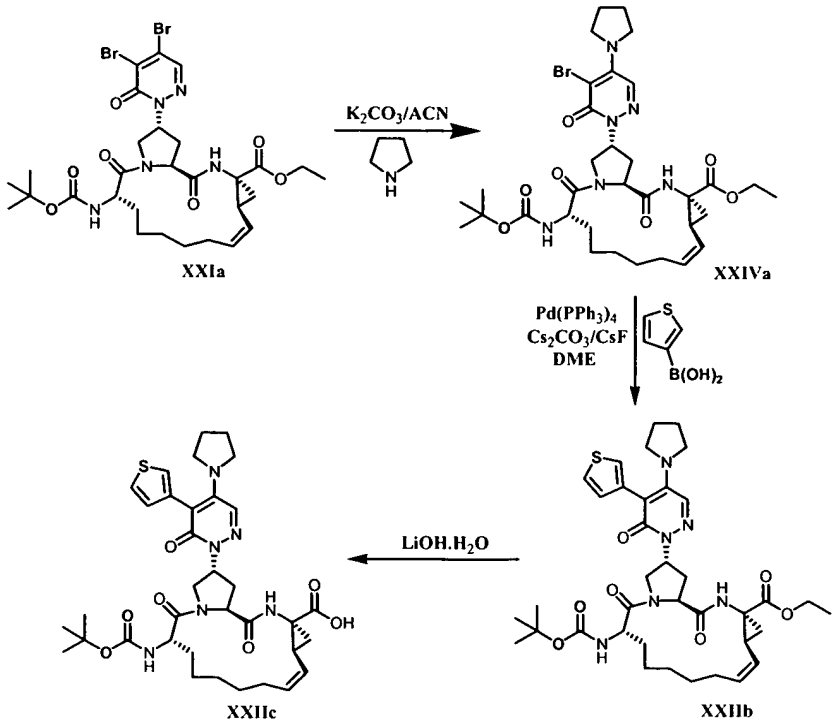
Scheme 21



The second method of preparing pyridazinone analogs of the present invention is to further chemically manipulate di-bromo intermediate XXIa (Scheme 21). The standard Mitsunobu coupling of the commercially available 4,5-dibromopyridazinone with hydroxyl If afforded the desired macrocycle XXIa. Coupling of XXIa with excess 3-thiophene boronic acid, cesium carbonate and potassium fluoride furnished di-thiophene XXIb. Hydrolysis of compound compounds XXIa and XXIb with LiOH gave the desired analogs XXId and XXIc respectively. Many different boronic acids may be used in a similar manner to yield a plethora of di-substituted pyridazinonyl macrocycles.

B. Bromide differentiation reaction

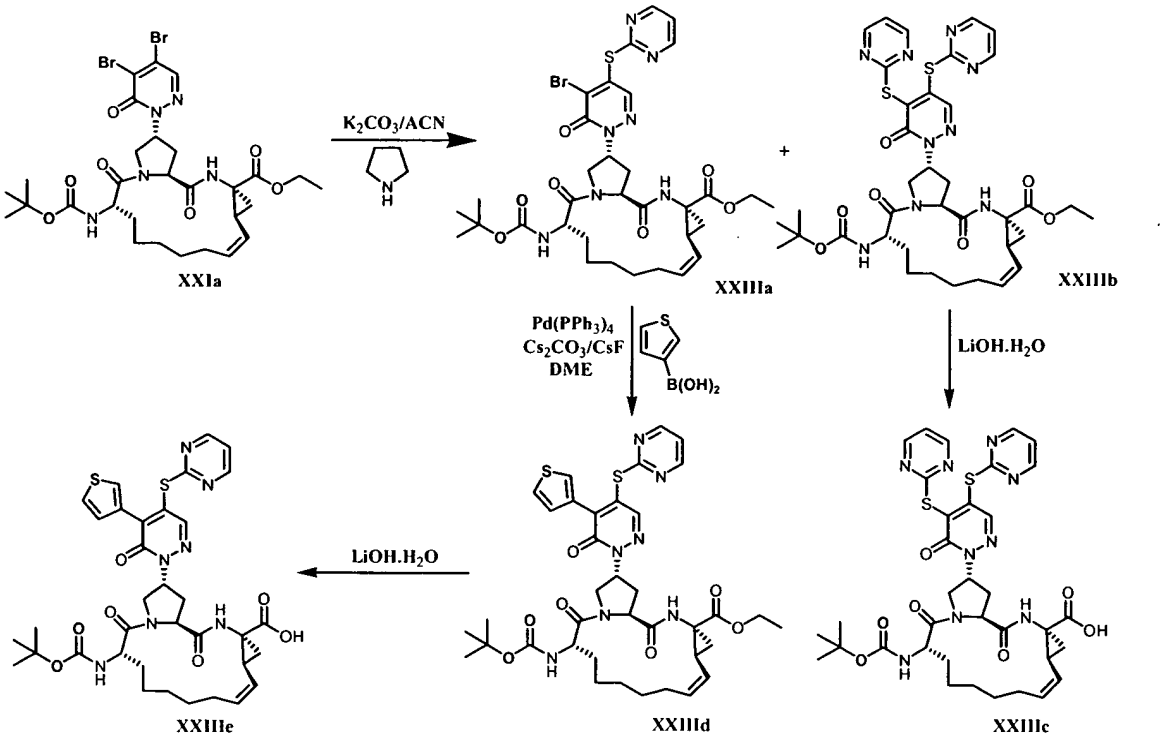
Scheme 22



Differentiation between the bromides on macrocyclic XXIa is achieved via Michael addition. As shown in Scheme 22, commercially available pyrrolidine is coupled with di-bromide to give compound XXIIa in 87% yield. The bromide moiety □ to the carbonyl is then under goes a Suzuki coupling reaction with 3-thiophene boronic acid to produce intermediate XXIIb, which is further treated with LiOH to afford analog XXIIc. For further details concerning the Suzuki coupling reaction see A. Suzuki, *Pure Appl. Chem.* 63, 419-422 (1991) and A. R. Martin, Y. Yang, *Acta Chem. Scand.* 47, 221-230 (1993).

C. Sulfur containing nucleophiles

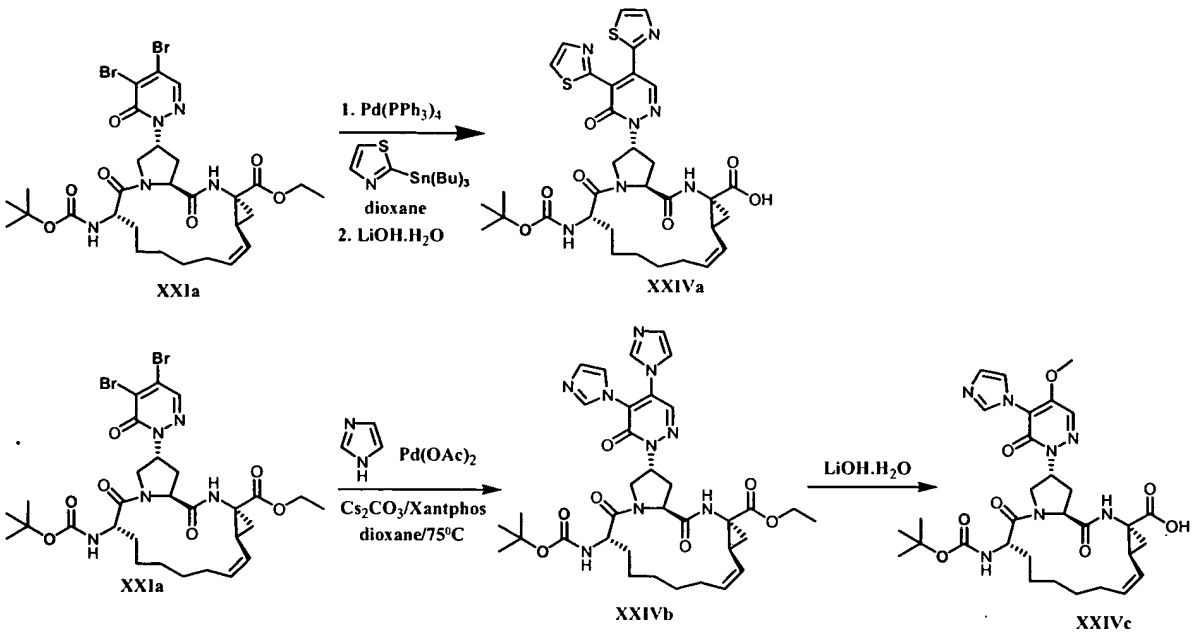
Scheme 23



While the secondary amine nucleophile pyrrolidine gave exclusive addition to the 5-bromide position on macrocycle XXIa, sulfur-containing nucleophiles did not exhibit the same selectivity as shown in Scheme 23. With sulfur-containing nucleophiles, addition on both bromines of XXIa is observed together with the mono-coupled product XXIIa with only one equivalent of mercaptopyrimidine. The separability of compounds XXIIIa, XXIIIB and starting material XXIa by flash column chromatography allowed for a further Suzuki coupling of the mono-alkylated XXIIIa with 3-thiophene boronic acid followed by hydrolysis of XXIIId with LiOH to furnish analog XXIIIe. The di-alkylated product XXIIIb is also hydrolyzed with LiOH to produce analog XXIIIc.

D. Suzuki coupling with boronic acid

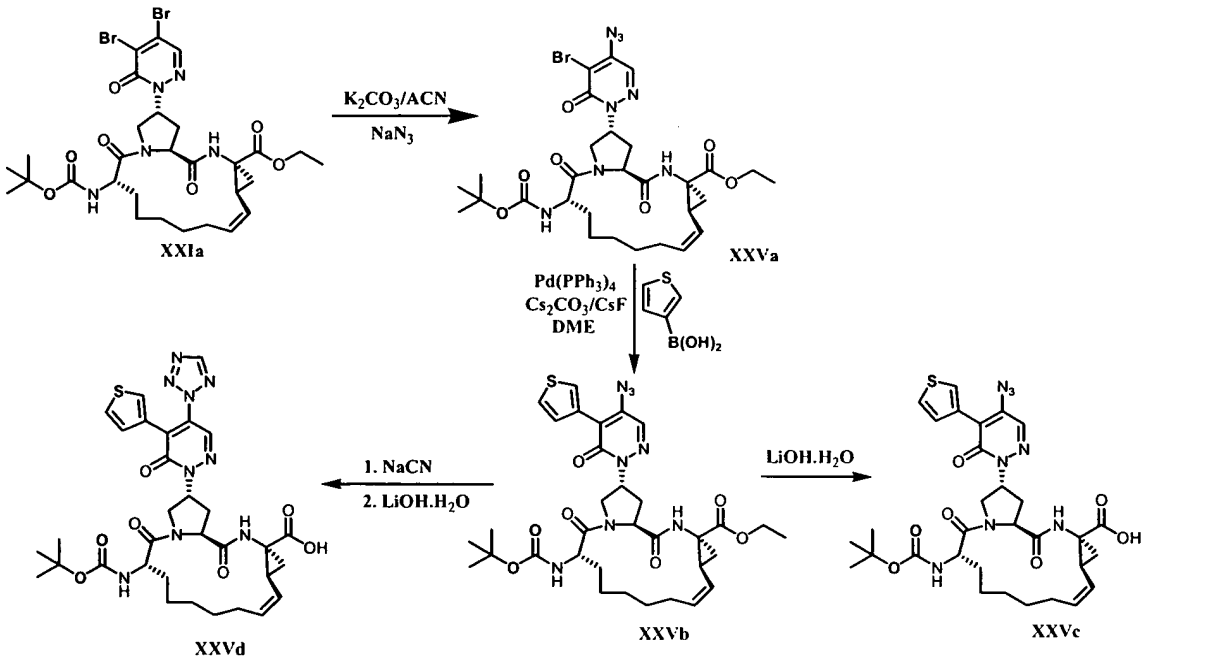
Scheme 24



With only a limited number of boronic acids available for Suzuki coupling, other coupling methods such as Stille coupling and N-arylation using Buchwald's chemistry were also explored (Scheme 24). Coupling of intermediate XXIa with 2-stannylthiazole with Stille standard conditions followed by hydrolysis afforded analog XXIVa. As for N-arylation, coupling of imidazole to di-bromide 6 proceeded smoothly. Unfortunately, hydrolysis with LiOH resulted in replacement of the imidazole moiety on position 5 with a methoxy (XXIVb. For further details concerning Stille coupling reactions see J. K. Stille, *Angew. Chem. Int. Ed.* 25, 508-524 (1986); M. Pereyre *et al., Tin in Organic Synthesis* (Butterworths, Boston, 1987) pp 185-207 *passim.*, and T. N. Mitchell, *Synthesis* 1992, 803-815. For further details of the Buchwald reaction see J. F. Hartwig, *Angew. Chem. Int. Ed.* 37, 2046-2067 (1998).

E. Other diversified pyridazinone analogs

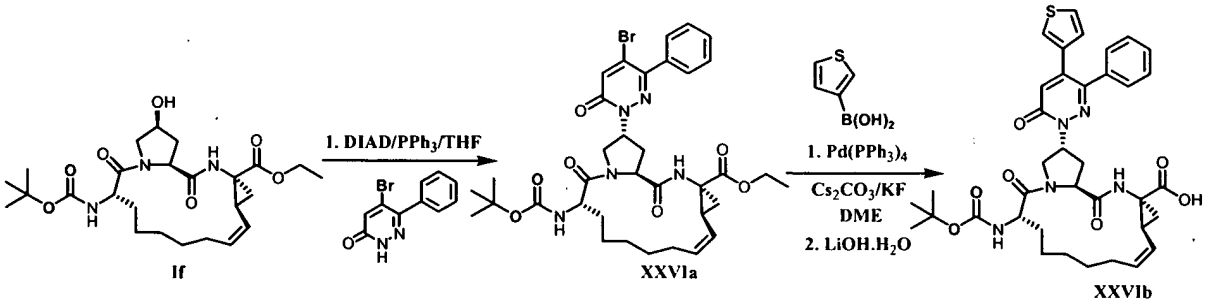
Scheme 25



Another method for diversifying pyridazinone analogs is outlined in Scheme 25. Michael addition with sodium azide as the nucleophile to di-bromo XXIa yielded, as in the secondary amine case, only the mono-coupled compoundXXVa. Further Suzuki coupling with 3-thiophene boronic acid produced azide XXVb. Compound XXVb is hydrolyzed to give analog XXVc. In addition, the azide moiety of compound XXVb is further converted to tetrazole under standard conditions with sodium cyanide, followed by hydrolysis to provide analog XXVd.

F. Synthesis of 5,6 pyridazinoyl macrocycle

Scheme 26



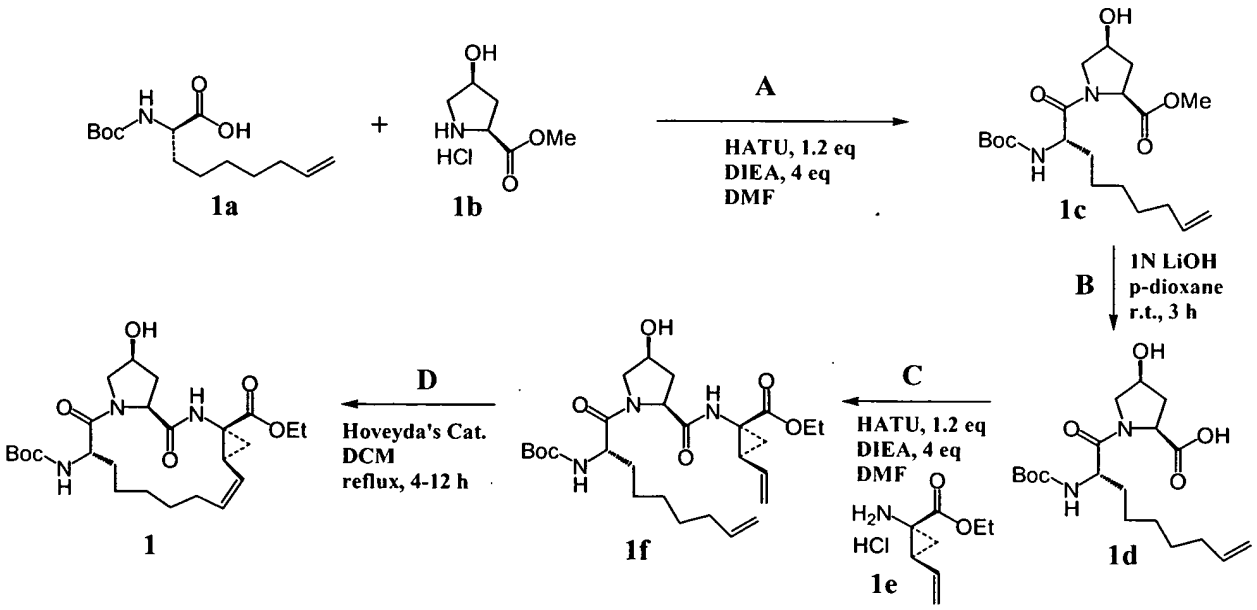
The synthesis of 5,6 pyridazinonyl macrocycle XXVIb is outlined in Scheme 26. Commercially available 5-bromo-6-phenyl-2H-pyridazin-3-one is condensed with key intermediate If *via* Mitsunobu conditions to give compound XXVIa. Product XXVIa is

further subjected to Suzuki coupling conditions with 3-thiophene boronic acid, followed by hydrolysis to give the desired analog XXVb.

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. Synthesis of the cyclic peptide precursor



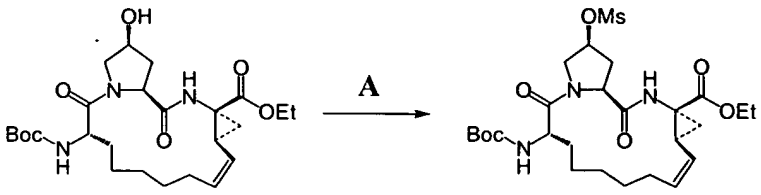
1A. To a solution of Boc-L-2-amino-8-nonenoic acid **1a** (1.36g, 5 mol) and the commercially available cis-L-hydroxyproline methyl ester **1b** (1.09g, 6 mmol) in 15 ml DMF, was added DIEA (4 ml, 4eq.) and HATU (4g, 2eq). The coupling was carried out at 0 °C over a period of 1 hour. The reaction mixture was diluted with 100 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then was evaporated, affording the dipeptide **1c** (1.91g, 95.8%) that was identified by HPLC (Retention time = 8.9 min, 30-70%, 90%B), and MS (found 421.37, $M+Na^+$).

1B. The dipeptide **1c** (1.91g) was dissolved in 15 mL of dioxane and 15 mL of 1 N LiOH aqueous solution and the hydrolysis reaction was carried out at RT for 4 hours. The reaction mixture was acidified by 5% citric acid and extracted with 100 mL EtOAc, and followed by washing with water 2x20 ml, 1M $NaHCO_3$ 2x20 ml and brine 2x20 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then removed in vacuum, yielding the free carboxylic acid compound **1d** (1.79g, 97%), which was used for next step synthesis without need for further purification.

1C. To a solution of the free acid obtained above (1.77, 4.64 mmol) in 5 ml DMF, D-β-vinyl cyclopropane amino acid ethyl ester **1e** (0.95g, 5 mmol), DIEA (4 ml, 4eq.) and HATU (4g, 2eq) were added. The coupling was carried out at 0 °C over a period of 5 hours. The reaction mixture was diluted with 80 mL EtOAc, and followed by washing with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and then evaporated. The residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (5:1→3:1→1:1→1:2→1:5). The linear tripeptide **1f** was isolated as an oil after removal of the elution solvents (1.59g, 65.4%), identified by HPLC (Retention time = 11.43 min) and MS (found 544.84, $M+Na^+$).

1D. Ring Closing Metathesis (RCM). A solution of the linear tripeptide **1f** (1.51g, 2.89 mmol) in 200 ml dry DCM was deoxygenated by bubbling N_2. Hoveyda's 1st generation catalyst (5 mol% eq.) was then added as solid. The reaction was refluxed under N_2 atmosphere 12 hours. The solvent was evaporated and the residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1→1:2→1:5). The cyclic peptide precursor **1** was isolated as a white powder after removal of the elution solvents (1.24g, 87%), identified by HPLC (Retention time = 7.84 min, 30-70%, 90%B), and MS (found 516.28, $M+Na^+$). For further details of the synthetic methods employed to produce the cyclic peptide precursor **1**, see U.S. Patent No. 6,608,027, which is herein incorporated by reference in its entirety.

Example 2. Synthesis of the cyclic peptide precursor mesylate

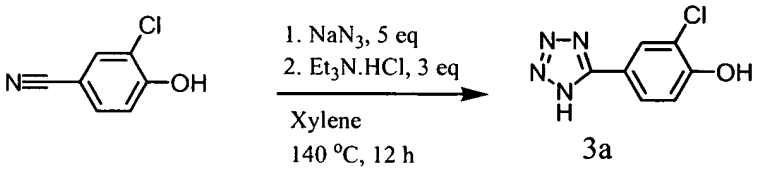


1 2

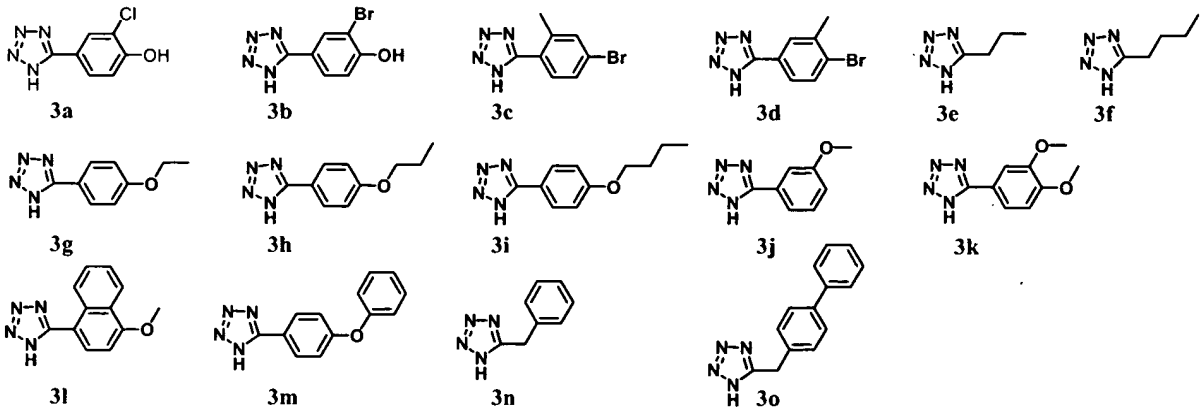
2A. To a solution of the macrocyclic peptide precursor **1** (500mg, 1.01 mmol) and DIEA (0.4 ml, 2 mmol) in 2.0 ml DCM, mesylate chloride (0.1 ml) was added slowly at 0 °C where the reaction was kept for 3 hours. 30 mL EtOAc was then added and followed by washing with 5% citric acid 2x10 ml, water 2x10 ml, 1M $NaHCO_3$ 2x10 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and evaporated, yielding the title compound mesylate that was used for next step synthesis without need for further purification.

Example 3. Tetrazole Synthesis

Structurally diverse tetrazoles IIIa-IIIq, for use in preparing tetrazolyl macrocycles of the invention were synthesized from commercially available nitrile compounds as described below:

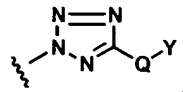


3a

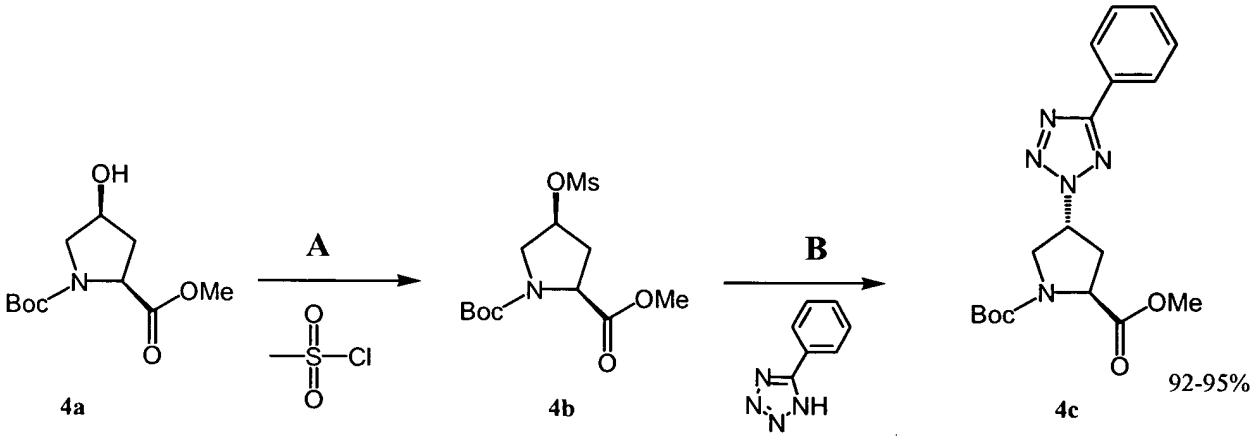


To a sealed tube containing 5 ml xylene, was added 3-Cl-4-hydroxy-benzoacetonitile (0.31g, 5 mol), NaN_3 (0.65g, 10 mmol) and the triethylamine hydrochloride (0.52g, 3 mmol). The mixture was stirred vigorously at 140 °C over a period of 20-30 hours. The reaction mixture was then cooled and poured to a mixture of EtOAc (30 ml) and aqueous citric acid solution (20 mL). After washing with water 2x10

ml and brine 2x10 ml, the organic phase was dried over anhydrous Na_2SO_4 and was evaporated to a yellowish solid. After re-crystallization with EtOAc-hexanes, the tetrazole compound **3a** was obtained in good yield (0.4g, 86%%), high purity (>90%, by HPLC), and identified by NMR and MS (found 197.35 and 199.38, $M+H^+$).

Example 4. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

PROLINE DERIVATIVE SYNTHESIS

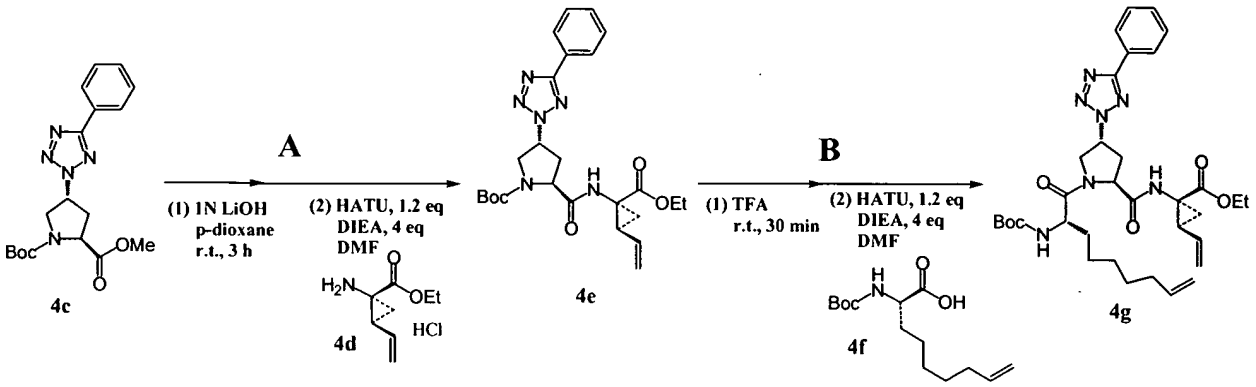


To a solution of N-Boc-cis-hydroxyproline methyl ester **4a** (10 g, 40.8 mmol) and N,N-Diisopropylethyl amine (DIEA, 12 mL, 60 mmol) in 110 mL of DCM, was added 3.85 mL of mesylate chloride (50 mmol) in a dropwise manner and the resulting reaction mixture was stirred at 0 °C for 3 hours. TLC (hexanes:ethyl acetate = 1:1, v/v) showed that Boc-cis-Hyp-OMe **4a** was totally converted to its mesylate **4b**. After the reaction was deemed complete by TLC, the reaction mixture was diluted with 100ml EtOAc, washed with 5% citric acid 2x50 ml and brine 2x30 ml, and dried over anhydrous Na_2SO_4. Removal of solvents gave 13 g (98% yield) N-Boc-cis-4-mesylate-proline methyl ester **4b**, which was used in Step **B** without need for further purification.

To a solution of the mesylate **4b** (0.65 g, 2 mmol) in 5 mL DMF, was added 4 mmol of 5-phenyl-1H-tetrazole and anhydrous sodium carbonate (0.53 g, 5 mmol). The resulting reaction mixture was stirred vigorously at 60°C for 6-12 hours. TLC (hexanes:ethyl acetate = 1:1, v/v) showed the mesylate **4b** was completely converted to trans 4-tetrazole-substituted proline derivative **4c**. After the reaction was deemed

complete by TLC, the reaction mixture was diluted with 30 ml EtOAc and washed with 1 M Na_2CO_3 (3x10 ml), water (3x10 ml), 5% citric acid (3x10 ml) and brine (3x10 ml), respectively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, giving the 5-phenyl tetrazole substituted proline derivative **4c** in excellent yield (94%) and high purity (>90%). **4c**: 94% yield, $[M+Na]^+$ = 396.39.

SYNTHESIS OF LINEAR TRIPEPTIDES

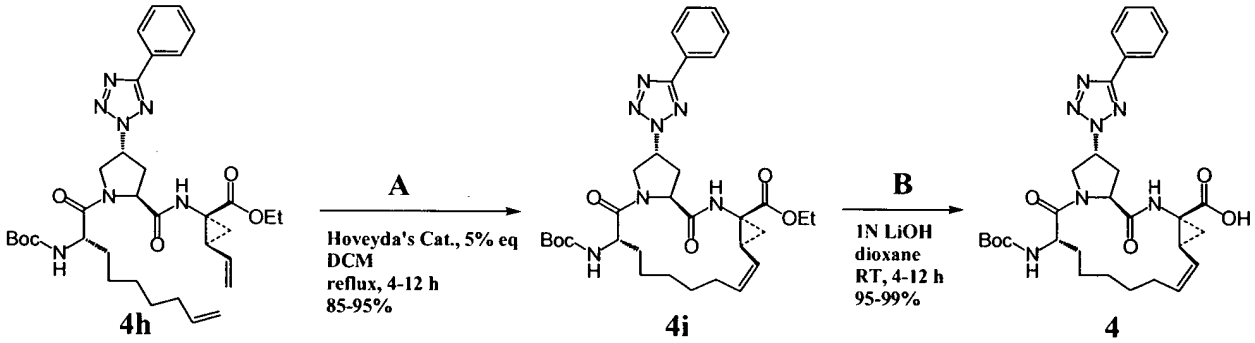


A. (1) The dipeptide **4e** was prepared by dissolving 0.22 g (0.6 mmol) of N-Boc-trans-4-(3-phenyl tetrazolyl)-proline methyl ester **4c** in 6 mL of dioxane and 2 mL of 1 N LiOH aqueous solution. The resulting reaction mixture was stirred at RT for 3-8 hours to allow the for the hydrolysis of the methyl ester. The reaction mixture was acidified by 5% citric acid, extracted with 40 mL EtOAc, and washed with water 2x20 ml, 1M $NaHCO_3$ 2x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, yielding the free carboxylic acid compound (0.20g, 92%), which was used for next step synthesis without need for further purification. **(2)** To a cooled (0 °C) solution of the free acid obtained above (0.20g, 0.55 mmol) in 2 ml DMF, was added D-β-vinyl cyclopropane amino acid ethyl ester **4d** (0.1g, 0.52 mmol), DIEA (0.4 ml, 4eq.) and HATU (0.4g, 2eq). The resulting reaction mixture was stirred at 0 °C for 0.5-3 hours. The reaction mixture was diluted with 40 mL EtOAc, and washed with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml, and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording the dipeptide **4e** (0.24g, 94%), identified by HPLC (Retention time = 10.03 min) and MS (found 519.22, $M+Na^+$).

B. (1) Tripeptide **4g** was prepared by deprotecting the amine of dipeptide **4e** (0.24 g, 0.49 mmol) in 2 mL TFA at 0 °C for 10 min. After removal of TFA *in vacuo*, the

free amine product was subjected to next coupling reaction directly. **(2)** To a cooled (0 °C) solution of the free amine compound obtained above in 2 ml DMF, was added Boc-2-amino-8-nonenoic acid **4f** (0.136g, 0.50 mmol), DIEA (0.4 ml, 4eq.) and HATU (0.4g, 2eq). The coupling was carried out at 0 °C over a period of 0.5-3 hours. The reaction mixture was diluted with 40 mL EtOAc and washed with 5% citric acid 2x 20 ml, water 2x20 ml, 1M $NaHCO_3$ 4x20 ml and brine 2x10 ml, respectively. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording tripeptide **4g** (0.28g, 88% for two steps) that was identified by HPLC (Retention time = 14.03 min), and MS (found 672.30, $M+Na^+$).

SYNTHESIS OF CYCLIC PEPTIDE VIA RING-CLOSING-METATHESIS (RCM).



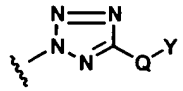
A. A solution of linear tripeptide **4g** (71mg, 0.109 mmol) in 50 ml dry DCM was deoxygenated by bubbling N_2. To the resulting degassed solution was added Hoveyda's Cat. (5-10 mol% eq.) was as solid and the resulting reaction mixture was refluxed under N_2 over for 5-20 hours. The reaction mixture was then concentrated *in vacuo* and the residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1→1:2). The macrocyclic peptide **4i** was isolated as a white powder by evaporation of the elution solvents (58mg, 85.5%), identified by HPLC (Retention time = 11.80 min, 30-80%, 90%B), and MS (found 644.66, $M+Na^+$).

IV. HYDROLYSIS OF THE ETHYL ESTER

The title compound was prepared by dissolving compound **4i** (20mg) in 2 mL of dioxane and 1 mL of 1 N LiOH aqueous solution. The resulting reaction mixture was stirred at RT for 4-8 hours. The reaction mixture was then acidified with 5% citric acid, extracted with 10 mL EtOAc, and washed with water 2x20 ml. The solvent was

evaporated and the residue was purified by HPLC on a YMC AQ12S11-0520WT column with a 30-80% (100% acetonitrile) gradient over a 20 min period. After lyophilization, title compound was obtained as a white amorphous solid.

[M+Na] + = 616.72.

Example 5. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 2-bromophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

5A. PROLINE DERIVATIVE SYNTHESIS

The proline derivative of the present example was prepared by the procedure set forth in Example 4 (I) with 5-(2-bromophenyl)-1H-tetrazole and N-Boc-cis-hydroxyproline methyl ester **4a**.

$[M+Na]^+ = 396.39$.

5B. SYNTHESIS OF LINEAR TRIPEPTIDES

The linear peptide of the present example was prepared via the procedure set forth in Example 4 (II) with the proline derivative prepared in step **5A**, D-β-vinyl cyclopropane amino acid ethyl ester, and Boc-2-amino-8-nonenoic acid.

$[M+H]^+ = 728.41$

5C. RING CLOSING METATHESIS

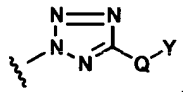
The macrocyclic peptide ethyl ester of the present example was prepared with the linear peptide of Step **5B** via the procedure set forth in Example 4 (III).

$[M+Na]^+ = 722.37$.

5D. HYDROLYSIS OF THE ETHYL ESTER

The title compound was ultimately obtained via hydrolyisis described in Example 4 (IV) from the ethyl ester of Step **5C**.

$[M+H]^+ = 672.49$.

Example 6. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-bromophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

6A. PROLINE DERIVATIVE SYNTHESIS

The proline derivative of the present example was prepared by the procedure set forth in Example 4 (I) with 5-(3-bromophenyl)-1H-tetrazole and N-Boc-cis-hydroxyproline methyl ester **4a**.

$[M+Na]^+ = 396.39$.

6B. SYNTHESIS OF LINEAR TRIPEPTIDES

The linear peptide of the present example was prepared via the procedure set forth in Example 4 (II) with the proline derivative prepared in step **6A**, D-β-vinyl cyclopropane amino acid ethyl ester, and Boc-2-amino-8-nonenoic acid.

$[M+H]^+ = 728.41$.

6C. RING CLOSING METATHESIS

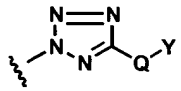
The macrocyclic peptide ethyl ester of the present example was prepared with the linear peptide of Step **6B** via the procedure set forth in Example 4 (III).

$[M+Na]^+ = 722.37$.

6D. HYDROLYSIS OF THE ETHYL ESTER

The title compound was ultimately obtained via hydrolyisis described in Example 4 (IV) from the ethyl ester of Step **6C**.

$[M+H]^+ = 672.49$.

Example 7. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-bromophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

7A. PROLINE DERIVATIVE SYNTHESIS

The proline derivative of the present example was prepared by the procedure set forth in Example 4 (I) with 5-(4-bromophenyl)-1H-tetrazole and N-Boc-cis-hydroxyproline methyl ester **4a**.

$[M+Na]^+ = 396.39$.

7B. SYNTHESIS OF LINEAR TRIPEPTIDES

The linear peptide of the present example was prepared via the procedure set forth in Example 4 (II) with the proline derivative prepared in step **7A**, D-β-vinyl cyclopropane amino acid ethyl ester, and Boc-2-amino-8-nonenoic acid.

$[[M+Na] +H]^+ = 728.41$.

7C. RING CLOSING METATHESIS

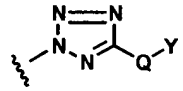
The macrocyclic peptide ethyl ester of the present example was prepared with the linear peptide of Step **7B** via the procedure set forth in Example 4 (III).

$[M+Na]^+ = 722.37$.

7D. HYDROLYSIS OF THE ETHYL ESTER

The title compound was ultimately obtained via hydrolyisis described in Example 4 (IV) from the ethyl ester of Step **7C**.

$[M+H]^+ = 672.49$.

Example 8. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 5-Bromo-2-thienyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

8A. PROLINE DERIVATIVE SYNTHESIS

The proline derivative of the present example was prepared by the procedure set forth in Example 4 (I) with 5-(5-Bromo-2-thienyl)-1H-tetrazole and N-Boc-cis-hydroxyproline methyl ester **4a**.

$[M+Na]^+ = 480.23$.

8B. SYNTHESIS OF LINEAR TRIPEPTIDES

The linear peptide of the present example was prepared via the procedure set forth in Example 4 (II) with the proline derivative prepared in step **8A**, D-β-vinyl cyclopropane amino acid ethyl ester, and Boc-2-amino-8-nonenoic acid.

$[M-Boc+H]^+ = 634.29$.

8C. RING CLOSING METATHESIS

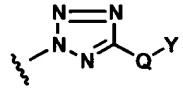
The macrocyclic peptide ethyl ester of the present example was prepared with the linear peptide of Step **8B** via the procedure set forth in Example 4 (III).

$[M+Na]^+ = 736.21$.

8D. HYDROLYSIS OF THE ETHYL ESTER

The title compound was ultimately obtained via hydrolysis described in Example 4 (IV) from the ethyl ester of Step **8C**.

$[M+H]^+ = 678.22$.

Example 9. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =2-bromo-4-pyridyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

9A. PROLINE DERIVATIVE SYNTHESIS

The proline derivative of the present example was prepared by the procedure set forth in Example 4 (I) with 5-(2-bromo-4-pyridyl)-1H-tetrazole and N-Boc-cis-hydroxyproline methyl ester **4a**.

$[M+Na]^+ = 453.23$.

9B. SYNTHESIS OF LINEAR TRIPEPTIDES

The linear peptide of the present example was prepared via the procedure set forth in Example 4 (II) with the proline derivative prepared in step **9A**, D-β-vinyl cyclopropane amino acid ethyl ester, and Boc-2-amino-8-nonenoic acid.

$[M-Boc+H]^+ = 629.31$.

9C. RING CLOSING METATHESIS

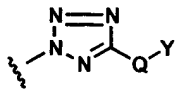
The macrocyclic peptide ethyl ester of the present example was prepared with the linear peptide of Step **9B** via the procedure set forth in Example 4 (III).

$[M+Na]^+ = 723.36$.

9D. HYDROLYSIS OF THE ETHYL ESTER

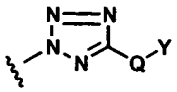
The title compound was ultimately obtained via hydrolysis described in Example 4 (IV) from the ethyl ester of Step **9C**.

$[M+H]^+ = 673.26$.

Example 10. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =2-biphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

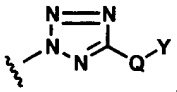
To a deoxygenated solution of ethyl ester compound from Step **5C** obtained above (40 mg), phenylboronic acid (10mg), KF (100mg), and Cs_2CO_3 (80mg) in 5 ml DME was added $Pd(PPh_3)_4$ (5mg) in its solid form. The resulting reaction mixture was heated in an oil bath to 90 °C and vigorously stirred for 6-12 hours. The solvent was evaporated and the residue was purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as the elution phase (9:1→5:1→3:1→1:1→2:1). The macrocyclic bi-aryl peptide ethyl ester was then isolated as a white powder by evaporation of the elution solvents (31mg, 78%) that was directly subjected to hydrolysis, as previously described in Example 4 (IV), and purified by HPLC.

$[M+Na]^+ = 692.38$.

Example 11. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =3-biphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

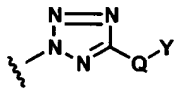
The title compound was prepared with the ethyl ester compound from Step **6C** and phenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+ = 692.38$.

Example 12. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =4-biphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

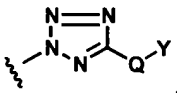
The title compound was prepared with the ethyl ester compound from Step **7C** phenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+ = 692.38$.

Example 13. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-(3-thienyl)phenyl , j = 3, m = s = 1, and $R^3 = R^4 = H$.

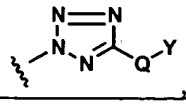
The title compound was prepared with the ethyl ester compound from Step **6C** and 3-thienylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+ = 698.32$.

Example 14. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-(p-trifluoromethoxyphenyl)phenyl , j = 3, m = s = 1, and $R^3 = R^4 = H$.

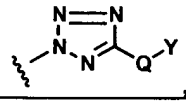
The title compound was prepared with the ethyl ester compound from Step **6C** and p-trifluoromethoxyphenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+ = 776.35$.

Example 15. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-(p-cyanophenyl)phenyl , j = 3, m = s = 1, and R^3 = R^4 = H.

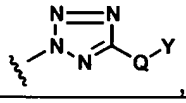
The title compound was prepared with the ethyl ester compound from Step **6C** and p-cyanophenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 692.38.

Example 16. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-(3-thienyl)phenyl , j = 3, m = s = 1, and R^3 = R^4 = H.

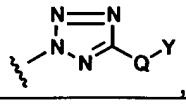
The title compound was prepared with the ethyl ester compound from Step **7C** and 3-thienylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 698.32.

Example 17. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-(p-trifluoromethoxyphenyl)phenyl , j = 3, m = s = 1, and R^3 = R^4 = H.

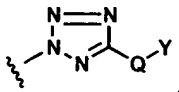
The title compound was prepared with the ethyl ester compound from Step **7C** and p-trifluoromethoxyphenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 776.35.

Example 18. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-(p-cyanophenyl)phenyl , j = 3, m = s = 1, and R^3 = R^4 = H.

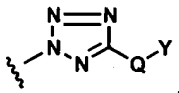
The title compound was prepared with the ethyl ester compound from Step **7C** and p-cyanophenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 692.38.

Example 19. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 5-phenyl-2-thienyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

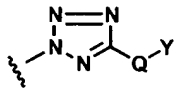
The title compound was prepared with the ethyl ester compound from Step **8C** and phenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 698.32.

Example 20. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 5-phenyl-3-pyridyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

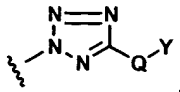
The title compound was prepared with the ethyl ester compound from Step **9C** and phenylboronic acid via the procedure set forth in Example 10, followed by hydrolysis of the ethyl ester according to the procedure of Example 4 (IV).

$[M+Na]^+$= 708.30.

Example 21. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, W is  , Q = absent, Y = 3-chloro-4-hydroxyphenyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

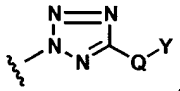
Replacement Method

The title compound was prepared via the replacement of the mesylate **2** and tetrazole **3a.** The replacement method is performed by dissolving 0.041mmol of the macrocyclic peptide precursor mesylate **2** and 0.123mmol of tetrazole **3a** in 3ml of DMF and adding 0.246mmol of sodium carbonate (60mg). The resulting reaction mixture is stirred at 60°C for 4-10 hours and subsequently cooled and extracted with ethyl acetate. The organic extract was washed with water (2x30ml), and the organic solution is concentrated *in vacuo* to be used in crude form for hydrolysis of the ethyl ester.

Example 22. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-hydroxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

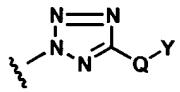
The title compound was prepared by dissolving the title compound of Example 4 (20mg) in 2 mL of dioxane and 1 mL of 1 N LiOH aqueous solution. The resulting reaction mixture was stirred at RT for 4-8 hours. The reaction mixture was acidified with 5% citric acid, extracted with 10 mL EtOAc, and washed with water 2x20 ml. The solvent was evaporated and the residue was purified by HPLC on a YMC AQ12S11-0520WT column with a 30-80% (100% acetonitrile) gradient over a 20 min period. After lyophilization, title compound was obtained as a white amorphous solid.

$[M+Na]^+$ = 666.24.

Example 23. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-bromo-4-hydroxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

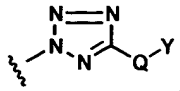
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3b** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ = 712.18.

Example 24. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 2-methyl-4-bromophenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

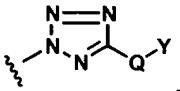
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3c** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ = 708.30.

Example 25. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-methyl-4-bromophenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

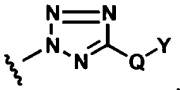
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3d** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ = 708.30.

Example 26. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =n-propyl, j = 3, m = s = 1, and R^3 = R^4 = H.

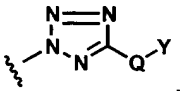
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3e** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ = 582.33.

Example 27. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y =n-butyl, j = 3, m = s = 1, and R^3 = R^4 = H.

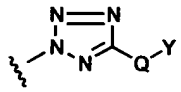
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3f** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ = 596.36.

Example 28. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-ethoxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

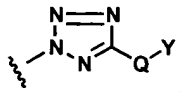
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3g** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+H]^+$ = 660.92.

Example 29. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-propoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

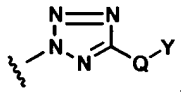
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3h** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 674.29$.

Example 30. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-butoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

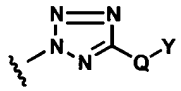
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3i** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 688.32$.

Example 31. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

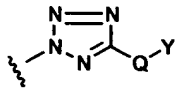
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3j** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 646.92$.

Example 32. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3,4-dimethoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

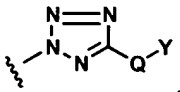
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3k** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 676.38$.

Example 33. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-methoxy-1-naphthyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

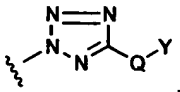
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3l** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 697.00$.

Example 34. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-phenoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

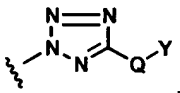
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3m** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 708.51$.

Example 35. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = benzyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

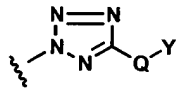
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3n** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 630.35$.

Example 36. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = p-phenylbenzyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

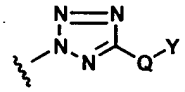
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and tetrazole **3o** from Example 3, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+ = 706.38$.

Example 37. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chlorophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

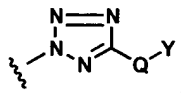
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-chlorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =650.33.

Example 38. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-fluorophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

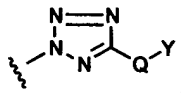
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-fluorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =634.37.

Example 39. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

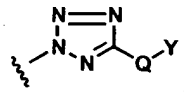
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-methoxyphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =646.92.

Example 40. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-phenoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

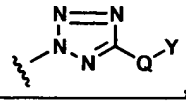
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-phenoxyphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =708.51.

Example 41. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-benzyloxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

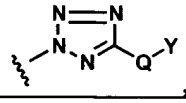
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-benzyloxyphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =722.32.

Example 42. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-trifluormethylphenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

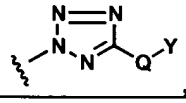
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-trifluormethylphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =684.32.

Example 43. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-bromophenyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

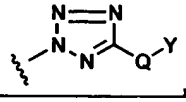
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-bromophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =696.28.

Example 44. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-fluorophenyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

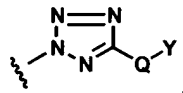
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-fluorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =634.36.

Example 45. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.

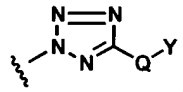
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-methoxyphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =646.36.

Example 46. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-ethoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

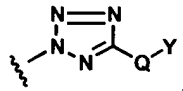
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-ethoxyphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+H]^+$ =660.92.

Example 47. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-trifluoromethylphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

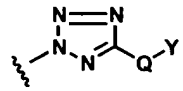
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-trifluoromethylphenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =684.32.

Example 48. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3,5-di(trifluoromethyl)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

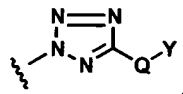
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3,5-di(trifluoromethyl)phenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =766.32.

Example 49. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-(N,N-dimethylamino)-3,5-di(trifluoromethyl)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

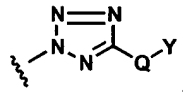
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-(N,N-dimethylamino)-3,5-di(trifluoromethyl)phenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =695.39.

Example 50. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 2,4-dichlorophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

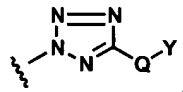
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(2,4-dichlorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =684.27.

Example 51. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3,5-dichlorophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

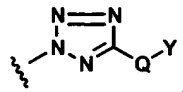
The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3,5-dichlorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =684.27.

Example 52. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3,4-dichlorophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3,4-dichlorophenyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

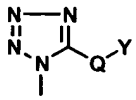
$[M+Na]^+$ =684.27.

Example 53. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 2-pyridyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(2-pyridyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =617.60.

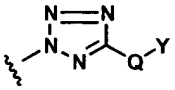
Example 54. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

W is  , Q = absent, Y = 2-pyridyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(2-pyridyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =617.60.

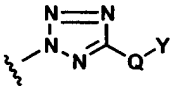
Example 55. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

W is  , Q = absent, Y = 3-pyridyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-pyridyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =645.24.

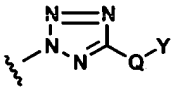
Example 56. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

W is  , Q = absent, Y = 4-pyridyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-pyridyl)-1H-tetrazole, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+H]^+$ =595.50.

Example 57. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

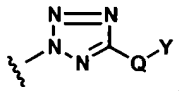
W is  , Q = absent, Y = 4-methoxy-3-bromophenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

57A. Tetrazole Formation

The tetrazole of the present example was prepared by dissolving 4-hydroxy-3-bromo-4-hydroxy-benzonitrile in DMF and adding methyl iodide and stirring at RT for 3-12 hours. The resulting reaction mixture was diluted with EtOAc and washed with water and brine. The resulting organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* to yield the 3-bromo-4-methoxy-benzonitrile. This compound then was used to form the corresponding tetrazole via the method described in Example 3.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(3-bromo-4-methoxy-phenyl)-1H-tetrazole from **57A**, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

$[M+Na]^+$ =724.91.

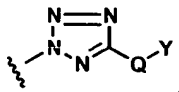
Example 58. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 4-(methylcyclopropane)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

58A. Tetrazole Formation

The tetrazole of the present example was prepared by dissolving 4-cyano-phenol in DMF and adding (bromomethyl)cyclopropane and stirring at RT for 3-12 hours. The resulting reaction mixture was diluted with EtOAc and washed with water and brine. The resulting organic phase was then dried over Na_2SO_4 and concentrated *in vacuo* to yield the 4-(methylcyclopropane)benzonitrile. This compound then was used to form the corresponding tetrazole via the method described in Example 3.

The title compound was prepared via the replacement method described in Example 21 with mesylate **2** and 5-(4-(methylcyclopropane)-phenyl)-1H-tetrazole from **58A**, followed by hydrolysis of the ethyl ester by the procedure of Example 22.

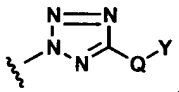
$[M+Na]^+$ =686.29.

Example 59. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-(methylcyclopropane)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The tile compound was prepared by using ethyl ester title compound from Example 21 without workup, adding (bromomethyl)cyclopropane, and stirring at 60°C

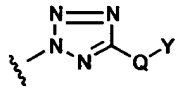
for 3-12 hours. The resulting reaction mixture was cooled to RT, poured into a mixture of 50:50 EtOAc:water, washed with water, and concentrated *in vacuo*. The resulting crude ethyl ester compound is then hydrolyzed to the free acid by the procedure set forth in Example 22.

$[M+Na]^+$ =720.24.

Example 60. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-methoxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

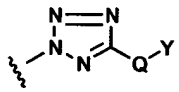
The title compound was prepared with the title compound of Example 21 and methyl iodide according to the procedure set forth in Example 59.

$[M+Na]^+$ =680.23.

Example 61. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-ethoxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

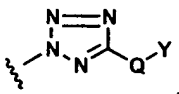
The title compound was prepared with the title compound of Example 21 and ethyl iodide according to the procedure set forth in Example 59.

$[M+Na]^+$ =694.28.

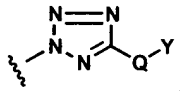
Example 62. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-bromo-4-ethoxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound was prepared with the ethyl ester precursor to the title compound of Example 23 and ethyl iodide according to the procedure set forth in Example 59.

$[M+Na]^+$ =740.17.

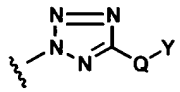
Example 63. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-(2-hydroxyethoxy)phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared with the title compound from Example 21 and 2-iodoethanol according to the procedure set forth in Example 59.

Example 64. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-bromo-4-(2-hydroxyethoxy)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

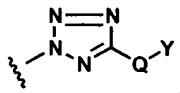
The title compound was prepared with the ethyl ester precursor to the title compound of Example 23 and 2-iodoethanol according to the procedure set forth in Example 59.

$[M+Na]^+ = 754.27$.

Example 65. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-(O-allyl)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

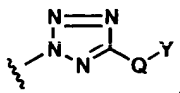
The title compound was prepared with the title compound from Example 21 and 3-iodopropene according to the procedure set forth in Example 59.

$[M+Na]^+ = 706.24$.

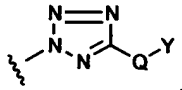
Example 66. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-bromo-4-(O-allyl)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared with the ethyl ester precursor to the title compound of Example 23 and 3-iodopropene according to the procedure set forth in Example 59.

$[M+Na]^+ = 752.15$.

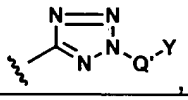
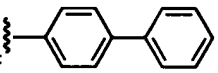
Example 67. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-(O-CH_2SCH_3)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

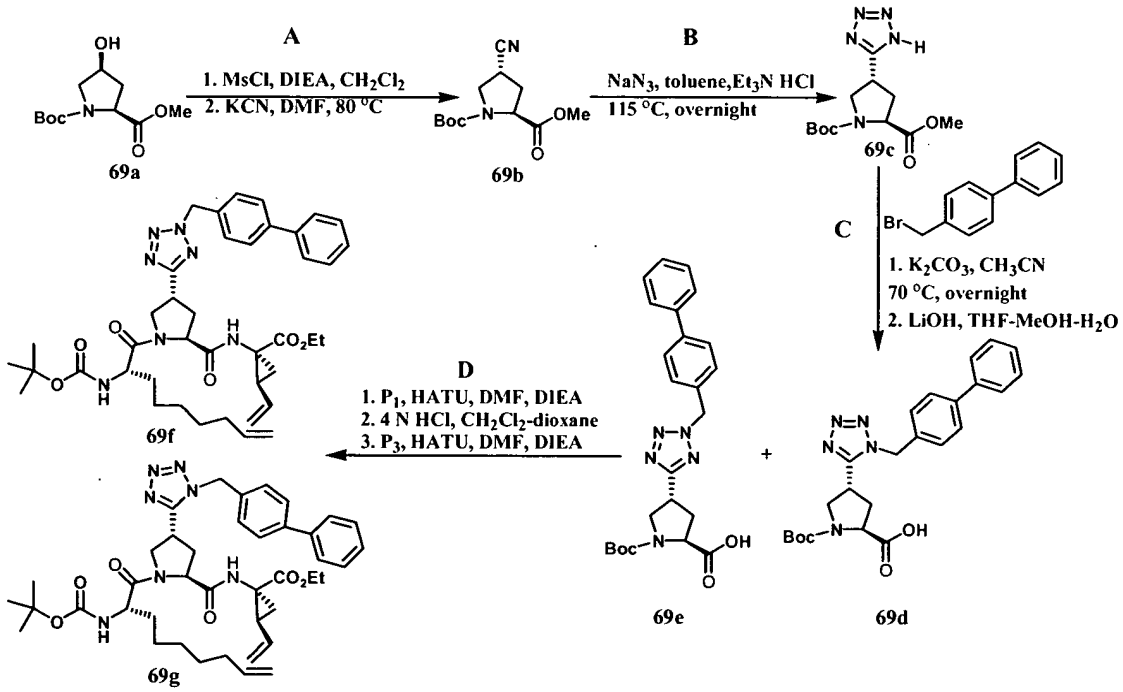
The title compound is prepared with the title compound from Example 21 and Cl–CH_2SCH_3 according to the procedure set forth in Example 59.

Example 68. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = 3-chloro-4-(O-CH_2SCH_3)phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared with the ethyl ester precursor to the title compound of Example 23 and Cl–CH_2SCH_3 according to the procedure set forth in Example 59.

$[M+Na]^+$ =752.15.

Example 69. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , wherein Q' = –CH_2–, Y =  , j = 3, m = s = 1, and $R^3 = R^4$= H.



69A. Preparation of Cyano Proline Derivative (**69b**)

To a solution of *cis*-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**69a**) (3.94 g, 16.06 mmol) in CH_2Cl_2 (40 ml) at 0 °C was DIEA (4.3 ml) and methanesulfonyl chloride (1.40 ml) dropwise. After addition, the mixture was stirred for 1.5 hours. The reaction was complete as determined by TLC analysis (50% EtOAc-hexane was used to develop the TLC). The mixture was diluted with EtOAc, washed

with *sat.* $NaHCO_3$, brine and dried (Na_2SO_4). After evaporation of the solvents, the oil residue was used for next step without further purification. $[M+H]^+ = 324$.

The crude product from the previous step was dissolved in DMF(35 ml) and grounded KCN (2.5 g) was added. The mixture was heated at 90 °C overnight. After cooled to room temperature, the mixture was diluted with EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. The crude product was purified by silica gel chromatography (20% EtOAc/hexane).

$[M+H]^+ = 255$.

69B. Preparation of Tetrazolyl Proline Derivative (**69c**)

To a solution of nitrile **69b** (669 mg, 2.63 mmol) in toluene (8 ml) was added NaN_3 (684 mg, 10.53 mmol) and Et_3N•HCl (1.45 g, 10.53 mmol). The mixture was heated at 115 °C for 18 hrs. The mixture was diluted with CH_2Cl_2, washed with 5% citric acid aqueous solution and dried over Na_2SO_4. Evaporation of solvent afforded the crude product **69c**•Et_3N additive (660 mg).

$[M+H]^+ = 298$.

69C. Preparation of the 5-Biphenylmethyl-tetrazolyl Proline (**69e**)

To a solution of **69c** (92.8 mg, 0.31 mmol) in THF (2 ml) was added 4-phenylbenzyl bromide (90.4 mg, 0.37 mmol) and K_2CO_3 (140 mg, 1.01 mmol). The mixture was heated at 65 °C overnight and then diluted with EtOAc, washed with brine, dried over Na_2SO_4. After evaporation of the solvent, the crude products was dissolved in THF-MeOH-H_2O (2 ml:1ml:1ml) and LiOH (130 mg) was added. The mixture was stirred at room temperature overnight. THF and MeOH were evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with 5% citric acid and dried with Na_2SO_4. Evaporation of solvent afforded the crude product **69d** and **69e**.

$[M+Boc+H]^+ = 350$.

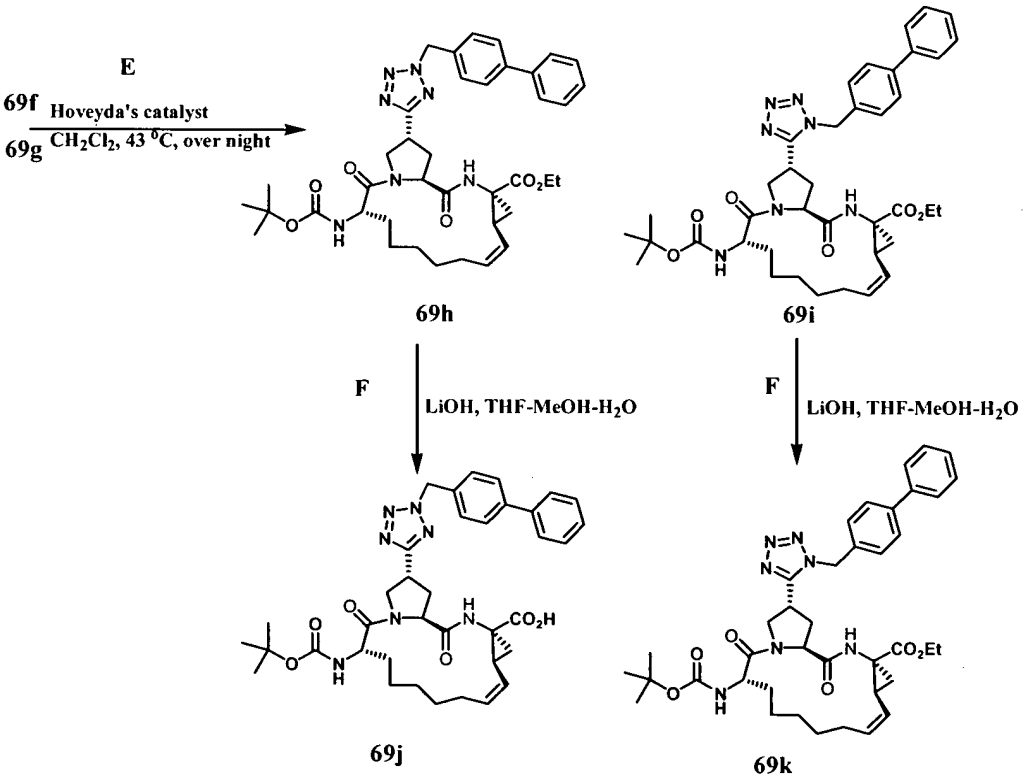
69D. Preparation of the Tripeptide (**69g**)

To a solution of **69d** and **69e** (about 0.31 mmol) in DMF (2.0 ml) was added D-β-vinyl cyclopropane amino acid ethyl ester•HCl (66 mg), DIEA (0.25 ml) and HATU (164 mg), sequentially. The mixture was stirred for 1 hr and then was diluted with EtOAc, washed with brine, 5% citric acid and dried with Na_2SO4. After evaporation of solvent,

the residue was dissolved in 2 ml of CH_2Cl_2, 2 ml of 4 N HCl in dioxane was added. The mixture was stirred at room temperature for 1.5 hr. solvent was evaporated. The residue was dissolved in EtOAc, neutralized with *sat.* $NaHCO_3$, washed with brine and dried with Na_2SO_4. After evaporation of solvent, the residue was dissolved in DMF (2 ml), to which P3 (120 mg), DIEA and HATU were added sequentially. The resulting mixture was stirred and monitored by TLC analysis. After the reaction was complete, the mixture was diluted with EtOAc, washed with brine, 5% citric acid, *sat.* $NaHCO_3$, and brine again. The organic solution was dried with Na_2SO_4, and evaporated under vacuum to give the crude product mixture which was purified by silica gel chromatography (30% to 50% EtOAc-Hexane).

$[M+H]^+ = 740$.

69E. Ring-Closing Metathesis (**69k**).



The mixture of **69f** and **69g** (60 mg) was dissolved in dry CH_2Cl_2 to make the concentration about 0.01 molar. The solution was carefully degassed with N_2 stream for 15 min. 5% mol of Hoveyda's catalyst was added under N_2. The mixture was refluxed overnight. Solvent was evaporated. The residue was loaded on silica gel column and eluted with 10% EtOAc to remove the catalyst. The two regioisomers were separated by

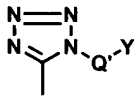
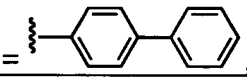
elution with 30-40% EtOAc-hexane to give a less polar product **69j** (37.9 mg) and more polar product **69k** (14.8 mg). The regiochemistry of **69j** and **69k** were determined by NMR analysis.

$[M+H]^+ = 712$.

69F. Ethyl Ester Hydrolysis (**69**)

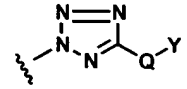
The ester **69h** (37.9 mg) was dissolved in THF-MeOH-H_2O (2 ml:1ml:1ml) and LiOH (21 mg) was added. The mixture was stirred at room temperature overnight. THF and MeOH were evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with 5% citric acid and dried with Na_2SO_4. Evaporation of solvent afforded the crude product. The crude product was purified by silica gel chromatography (5%MeOH in CH_2Cl_2) to give the title compound **69k**.

$[M+H]^+ = 684$.

Example 70. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is  , wherein Q' = $-CH_2-$, Y =  , j = 3, m = s = 1, and $R^3 = R^4 =$ H.

The ester **69i** (14.8 mg) was dissolved in THF-MeOH-H_2O (2 ml:1ml:1ml) and LiOH (21 mg) was added. The mixture was stirred at room temperature overnight. THF and MeOH were evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with 5% citric acid and dried with Na_2SO_4. Evaporation of solvent afforded the crude product. The crude product was purified by silica gel chromatography (5%MeOH in CH_2Cl_2) to give title compound **70**.

$[M+H]^+ = 684$.

Example 71. Compound of Formula II, wherein A = $-(C=O)-O-R^1$, wherein R^1 = cyclopentyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

71a – Amine deprotection.

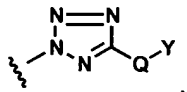
0.041mmol of the title compound of Example 21 is dissolved in 4ml of a 4M solution of HCl in dioxane and stirred for 1 hour. The reaction residue **69a** is concentrated *in vacuo*.

71b – Chloroformate Reagent

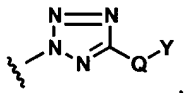
The chloroformate reagent **71b** is prepared by dissolving 0.045mmol of cyclopentanol in THF (3ml) and adding 0.09mmol of phosgene in toluene (20%). The resulting reaction mixture is stirred at room temperature for 2 hours and the solvent is removed *in vacuo*. To the residue is added DCM and subsequently concentrated to dryness twice *in vacuo* yielding chloroformate reagent **71b**.

71c – Carbamate formation

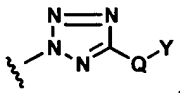
The title carbamate is prepared by dissolving residue **71a** in 1ml of THF, adding 0.045mmol of TEA, and cooling the resulting reaction mixture to 0°C. To this 0°C reaction mixture is added chloroformate reagent **71b** in 3ml of THF. The resulting reaction mixture is reacted for 2 hours at 0°C, extracted with EtOAc, washed by 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by procedure set forth in Example 22.

Example 72. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclobutyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

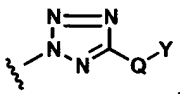
The title compound is prepared by the method described in Example 71 with the title compound of Example 21 and cyclobutanol, followed by ethyl ester hydrolysis by the procedure set forth in Example 22.

Example 73. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclohexyl, G = OH, L = absent W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

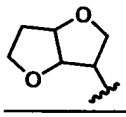
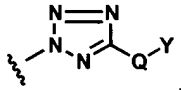
The title compound is prepared by the method described in Example 71 with the title compound of Example 21 and cyclohexanol, followed by ethyl ester hydrolysis by the procedure set forth in Example 22.

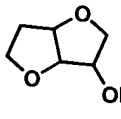
Example 74. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

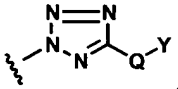
The title compound is prepared by the method described in Example 71 with the title compound of Example 21 and (R)-3-hydroxytetrahydrofuran, followed by ethyl ester hydrolysis by the procedure set forth in Example 22.

Example 75. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by the method described in Example 71 with the title compound of Example 21 and (S)-3-hydroxytetrahydrofuran, followed by ethyl ester hydrolysis by the procedure set forth in Example 22.

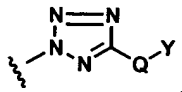
Example 76. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by the method described in Example 71 with the title compound of Example 21 and  , followed by ethyl ester hydrolysis by the procedure set forth in Example 22.

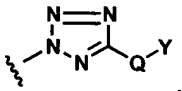
Example 77. Compound of Formula II, wherein A = –(C=O)–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 21 in 4ml of a 4M solution of HCl in dioxane and stirring the reaction mixture for 1 hour. The reaction residue is concentrated *in vacuo*. To this residue, 4ml of THF and 0.045mmol of TEA is added, the mixture is cooled to 0°C, to which is added

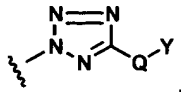
0.045mmol of the cyclopental acid chloride. The resulting reaction mixture is stirred for 2 hours at 0°C. The reaction mixture is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 22.

Example 78. Compound of Formula II, wherein A = –(C=O)–NH–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

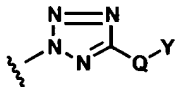
The title compound is prepared by dissolving 0.041mmol of the title compound from Example 21 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 22.

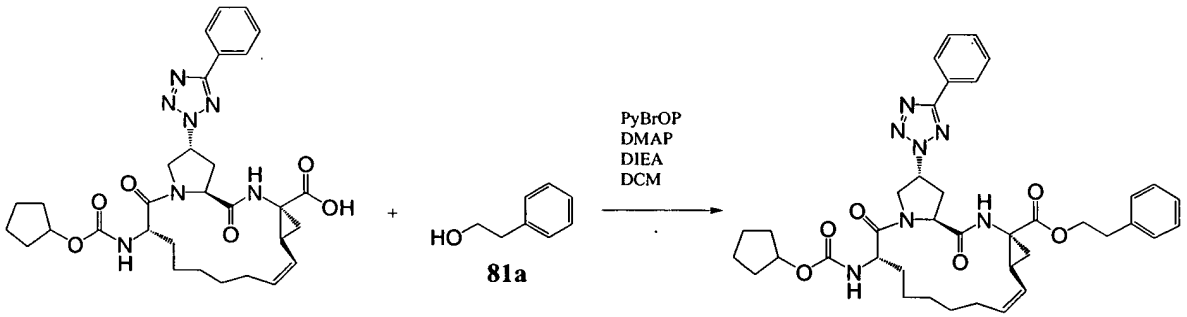
Example 79. Compound of Formula II, wherein A = –(C=S)–NH–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 21 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isothiocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 22.

Example 80. Compound of Formula II, wherein A = $-S(O)_2-R^1$, wherein R^1 = cyclopentyl, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 21 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. To the resulting concentrated reaction residue, which has been dissolved in 4ml THF, is added 0.045mmol of TEA, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl solfonyl chloride and the resulting reaction mixture is stirred at 0°C for 2 hours. The solution is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 22.

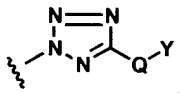
Example 81. Compound of Formula II, wherein A = $-(C=O)-O-R^1$, R^1 = cyclopentyl, G = –O–phenethyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.

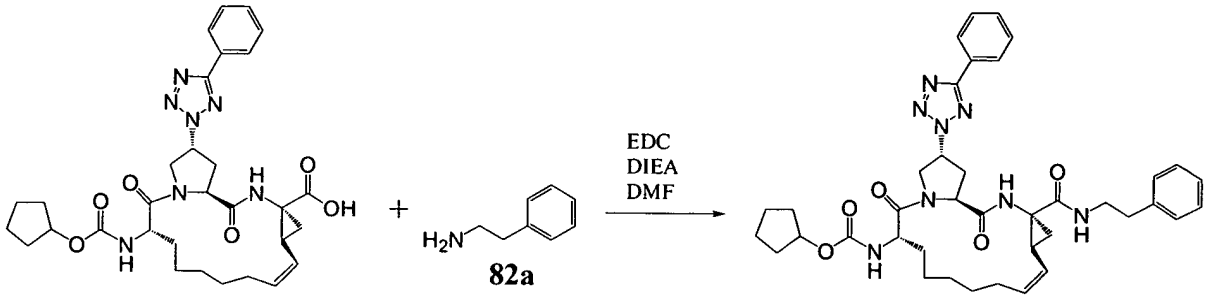


71 81a 81b

The title compound is prepared by adding to a solution of the title compound of Example 71 and phenethyl alcohol **81a** in 0.5 ml DCM, is added 1.2 eq. PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at °0 C. The resulting reaction mixture is stirred for 1 hour at 0°C and then warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated phenethyl ester **81b**.

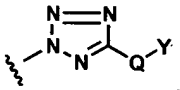
Other esters can be made using the same procedure.

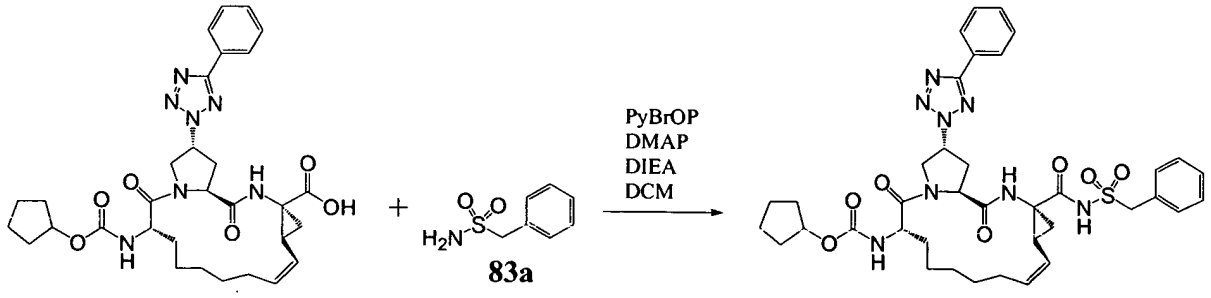
Example 82. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –NH–phenethyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.



71 82a 82b

The title compound is prepared by adding to a solution of the title compound of Example 71 and phenethylamine **82a** (0.05 ml) in 0.5 ml DMF, EDC (1.2 eq.) and DIEA (4eq.) at °0 C. The resulting reaction mixture is stirred at 1 hour. Subsequently, the reaction is warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford title compound phenethyl amide **82b**. Other amides can be made using the same procedure.

Example 83. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –NHS(O)$_2$–phenethyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.

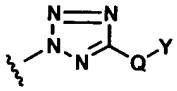


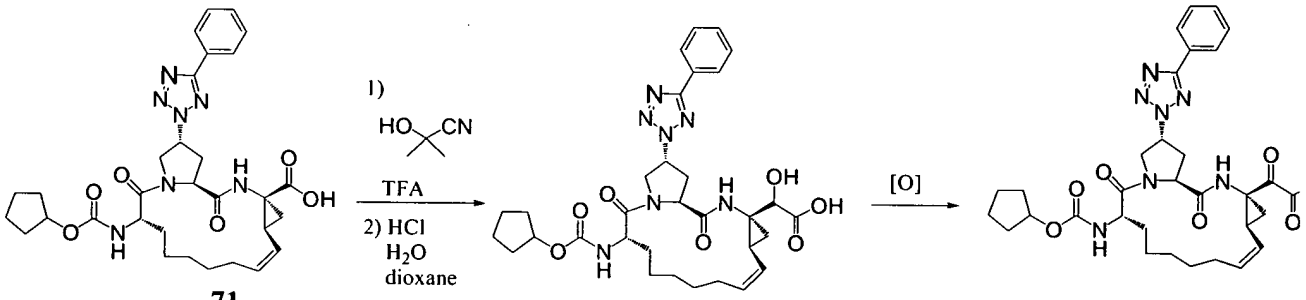
71 83a 83b

The title compound is prepared by adding to a solution of the title compound of Example 71 and α-toluenesulfonamide **83a** (10mg) in 0.5 ml DCM, is added 1.2 eq.

PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at °0 C. The resulting reaction mixture is stirred for 1 hour and then allowed to warm to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound sulfonamide **83c**.

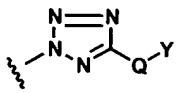
Other sulfonamides can be made using the same procedure.

Example 84. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

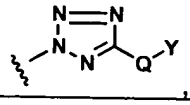


71 **84a** **84b**

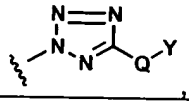
The title compound is prepared by adding to a solution of the title compound of Example 71 in 0.5 ml THF, is added α-hydroxy-α-methyl-propionitrile (0.1 ml) and catalytic amount TFA at 0°C. The resulting reaction mixture is warmed from °0 C to RT over a period of 4-12 h followed by hydrolysis with concentrated hydrochloric acid in dioxane. The reaction is then extracted with EtOAc, and washed with water and brine to yield α-hydroxy compound **83a** in its crude form. The crude compound **84a** undergoes a Dess-Martin oxidation in THF (0.5 ml), providing the α-carbonyl compound **84b** in crude form. The crude **84b** is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated keto acid **84b**.

Example 85. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–O–phenethyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

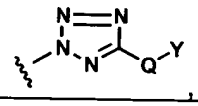
The title compound is prepared with the title compound keto acid of Example 84 and phenethanol according to the procedure set forth in Example 81.

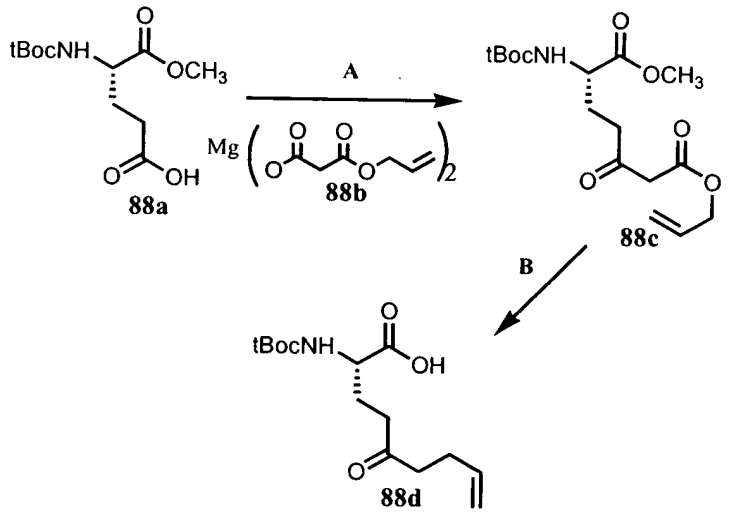
Example 86. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–NH–phenethyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared with the title compound keto acid of Example 84 and phenethyl amine according to the procedure set forth in Example 82.

Example 87. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–NH–$S(O)_2$–benzyl, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared with the title compound keto acid of Example 84 and α-toluenesulfonamide according to the procedure set forth in Example 83.

Example 88. Compound of Formula II, wherein A = tBOC, G = OH, L = –(C=O)CH_2–, W is  , Q = absent, Y = phenyl, j = 1, m = s = 1, and R^3 = R^4 = H.



Synthesis of (2*S*)-N-Boc-amino-5-oxo-non-8-enoic acid

88A. The aforementioned amino acid is prepared by adding to a solution of monoallyl ester of malonic acid in dry THF under N_2 at -78°C, n-Bu_2Mg dropwise over a

period of 5min. The resulting suspension is then stirred at RT for 1 hour and evaporated to dryness. Solid Mg salt **88b**, is dried under vacuum.

Glutamic acid derivative **88a** is first mixed with 1,1'-carbonyldiimidazole in anhydrous THF and the mixture is stirred at RT for 1h to activate the free acid moiety. Subsequently, the activated glutamic acid derivative is cannulated into a solution of Mg salt **88b** and the reaction mixture obtained is stirred at RT for 16h. The mixture then is diluted with ethyl acetate and the organic solution is washed with 0.5 N HCl (at 0°C) and brine, dried and evaporated. The residue obtained is resolved via silica chromatography with a 35-40% ethyl acetate in hexanes eluent system to yield diester **88c**.

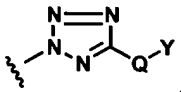
88B. To a stirred solution of tetrakis (triphenylphosphine) PD (0) in dry DMF is added the diester in DMF. The mixture is stirred at RT for 3.5 hours. The DMF is evaporated under reduced pressure and the residue diluted with EtOAc. The EtOAc solution is washed with 0.5N 0°C HCl, brine, dried and evaporated. The residue is chromatographed on silica gel using 15% to 20% EtOAc in hexane as eluent to afford the methyl ester intermediate.

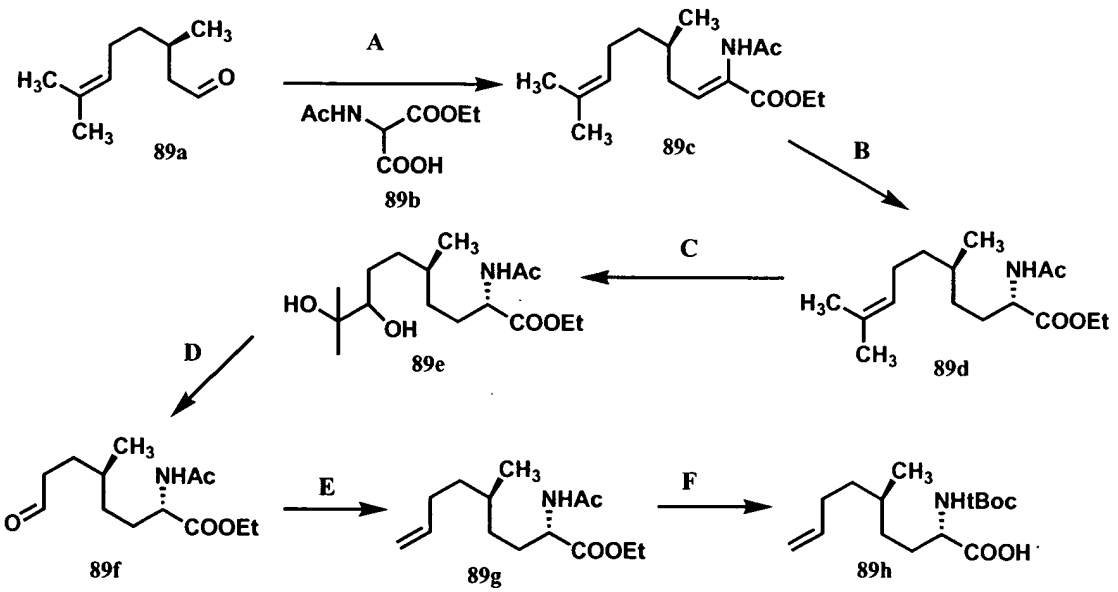
The methyl ester intermediate is then diluted with THF and water, $LiOH \bullet H_2O$ is added and the resulting mixture is stirred at RT for 25 hours, wherein the completion of the hydrolysis is monitored by TLC. The reaction mixture is concentrated under vacuum to remove a majority of the THF and further diluted with methylene chloride. The resulting solution is washed with 1 N HCl, dried with anhydrous Na_2SO_4 and concentrated under vacuum. To remove minor impurities and excess Boc_2O, the crude product is purified via flash chromatography using a solvent gradient from 100% hexane → 100% EtOAc as the eluent. (2*S*)-N-Boc-amino-5-oxo-non-8-enoic acid **88d** is obtained. For further details of the preceding amino acid synthesis may be found in T. Tsuda et al., *J. Am. Chem. Soc.*, **1980**, *102*, 6381-6384 and WO 00/59929, which are herein incorporated by reference in their entirety.

88C. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using (2*S*)-N-Boc-amino-5-oxo-non-8-enoic acid **88d** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **88C** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 89. Compound of Formula II, wherein A = tBOC, G = OH, L = $-CH(CH_3)CH_2-$, W is  , Q = absent, Y = phenyl, j = 1, m = s = 1, R^3 = methyl, and R^4 = H.



Synthesis of (2*S*, 5*R*)-N-Boc-2-amino-5-methyl-non-8-enoic acid (**89h**).

89A. To solid ethyl 2-acetamidomalonate **89b** is added (R)-(+)-citronellal **89a** in a solution of pyridine over 1 min. The resulting solution is cooled in a 10°C bath and acetic anhydride is added over 4 min. The resulting solution is stirred for 3 h at RT and another portion of ethyl 2-acetamidomalonate **89a** is added. The resulting mixture is stirred at RT for an additional 11 hours. Ice is then added and the solution is stirred for 1.5 hours, then the mixture is diluted with 250 ml water and extracted with two portions of wther. The organic phase is washed with 1N HCl, sat. $NaHCO_3$, dried Na_2SO_4,

concentrated and purified by flash chromatography (40% EtOAc/hexane) to afford compound **89c**.

89B. To a degassed solution of **89c** in dry ethanol is added (*S*,*S*)-Et-PUPHOS Rh(COD)OTf. The mixture is subjected to 30 psi of hydrogen and stirred on a Parr shaker for 2 hours. The resulting mixture is evaporated to dryness to obtain the crude compound **50d**, which is used in the subsequent step without purification.

89C. Compound **89d** is dissolved in a mixture of tBuOH/acetone/H_2O (1:1:1) and placed in an ice bath (0°C). NMMO and OsO_4 is consecutively added and the reaction mixture is stirred at RT for 4 hours. A majority of the acetone is removed by evaporation under vacuum and then the mixture is extracted with ethyl acetate. The organic layer is further washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The diol **50e** is obtained in high purity after flash column chromatography using 1% ethanol in ethyl acetate as the eluent.

89D. To a solution of diol **89e** in THF/H_2O (1:1) at 0°C, $NaIO_4$ is added and the reaction mixture is stirred at RT for 3.5 hours. A majority of the THF solvent is subsequently removed by evaporation under vacuum and the remaining mixture is extracted with EtOAc. The combined organic layers is further washed with 5% aqueous citric acid solution, 5% aq. $NaHCO_3$ and brine, then the organic phase is dried over $MgSO_4$ and evaporated to dryness under vacuum. Aldehyde intermediate **89f** is used in the following step in its crude form.

89E. To a solution of Ph_3PCH_3Br in anhydrous toluene, KHMDS is added forming a suspension which is stirred at RT for 30 min. under N_2. After stirring, the suspension is cooled to 0°C, a solution of aldehyde intermediate **89f** in THF is added, the mixture is warmed to RT, and stirred for 1 hour. A majority of the THF is evaporated under vacuum, EtOAc is added to the mixture and the organic phase is washed with water, 5% aq. $NaHCO_3$ and brine. The organic phase is then dried over $MgSO_4$ and evaporated to dryness under vacuum. Pure compound **89g** is isolated after purification via flash chromatography on silica gel, using hexane:EtOAc (3:2) as the eluent.

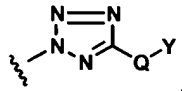
89F. To a solution of crude **89g** in THF, Boc_2O, and DMAP is added and the reaction mixture is heated to reflux for 2.5 hours. Subsequently, a majority of the THF is evaporated, the crude mixture is diluted with methylene chloride and washed with 1 N

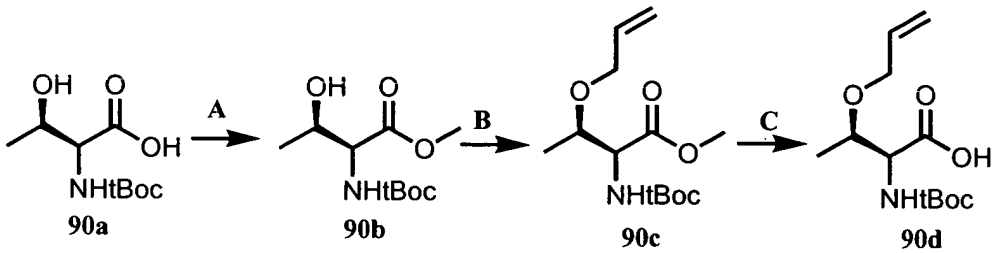
HCl to remove DMAP. The organic layer is further extracted with saturated aq. $NaHCO_3$, dried with anyhrous Na_2SO_4 and concentrated under vacuum. The crude product is then diluted with THF and water, $LiOH•H_2O$is added and the resulting mixture is stirred at RT for 25 hours, wherein the completion of the hydrolysis is monitored by TLC. The reaction mixture is concentrated under vacuum to remove a majority of the THF and further diluted with methylene chloride. The resulting solution is washed with 1 N HCl, dried with anhydrous Na_2SO_4 and concentrated under vacuum. To remove minor impurities and excess Boc_2O, the crude product is purified via flash chromatography using a solvent gradient from 100% hexane → 100% EtOAc as the eluent. (2*S*, 5*R*)-N-Boc-2-amino-5-methyl-non-8-enoic acid **89h** is obtained. For further details of the preceding amino acid synthesis see WO 00/59929, which is herein incorporated by reference in its entirety.

89G. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using ((2*S*, 5*R*)-N-Boc-2-amino-5-methyl-non-8-enoic acid **89h** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **89G** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 90. Compound of Formula II, wherein A = tBOC, G = OH, L = –O–, W is  , Q = absent, Y = phenyl, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.



Synthesis of *N* – Boc-*O*-allyl-(L)-threonine (**90d**)

90A. Boc-(L)-threonine **90a** is partially dissolved in methylene chloride/methanol at 0°C. A solution of diazomethane in diethyl ether is added until yellow, indicating the presence of diazomethane. Upon evaporation of the solvents, crude methyl ester **90b** is obtained.

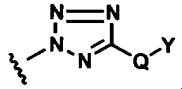
90B. Intermediate **90b** is dissolved in anhydrous diethyl ether, Ag_2O is added and freshly activated 4Å molecular sieves. Finally, allyl iodide is added to the reaction mixture and is stirred at reflux. Two additional portions of allyl iodide are added to the reaction mixture after a period of 20 hours and 30 hours and stirring is continued for a total of 36 hours. The mixture is then filtered through celite and purified by flash chromatography on silica gel, using EtOAc/hexane (1:4) as the eluent, to afford compound **90c**.

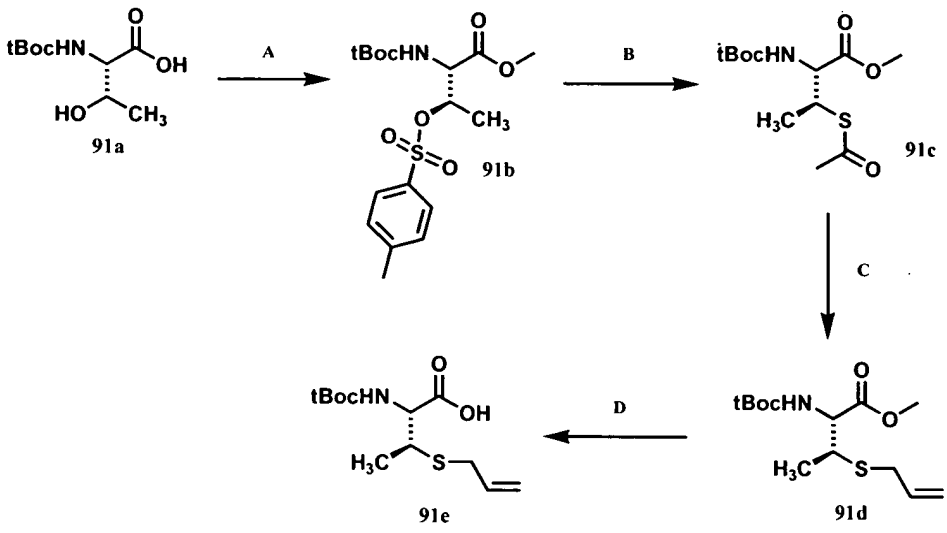
90C. Compound **90c** is dissolved in a mixture of THF/MeOH/H_2O (2:1:1) and LiOH•H_2O is added. The solution is stirred at RT for 2h, and the is acidified with 1 N HCl to pH ~3 before the solvents are removed under vacuum. The resulting crude compound **90d** is obtained. For further details of the preceding amino acid synthesis see WO 00/59929, which is herein incorporated by reference in its entirety.

90D. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using *N* – Boc-*O*-allyl-(L)-threonine **90d** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **90D** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 91. Compound of Formula II, wherein A = tBOC, G = OH, L = –S–, W is  , Q = absent, Y = phenyl, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.



Synthesis of (2*S*, 3*S*)-*N*-Boc-2 amino-3(mercaptoallyl)butanoic acid (**91e**).

91A. Compound **91a** is dissolved in pyridine and the solution is cooled to 0°C in an ice bath, tosyl chloride is added in small portions and the reaction mixture is partitioned between diethyl ether and H_2O. The ether layer is further washed with 0.2 N HCl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness under vacuum. Purification of the crude material by flash chromatography on silica gel, using hexane/EtOAc (gradient from 8:2 to 7:3 ratio) as the eluent, led to isolation of tosyl derivative **91b**.

91B. To a solution of tosyl derivative **91b** in anhydrous DMF, potassium thioacetate is added and the reaction mixture is stirred at RT for 24 hours. A majority of the DMF is then evaporated under vacuum and the remaining mixture is partitioned between EtOAc and H_2O. The aqueous layer is re-extracted with EtOAc, the combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. Purification of the crude material by flash chromatography on silica gel using hexane/EtOAc (4:1 ratio) as the eluent, affords thioester **91c**.

91C. To a solution of thioester **91c** is H_2O/EtOH (3:5 ratio) and aqueous solution of 0.2M NaOH is added and the mixture is stirred at RT for 1.5 hours. Allyl iodide is then added and stirring is continued at RT for an additional 30 min. The reaction mixture is concentrated to half of its original volume and then extracted with EtOAc. The aqueous layer is acidified to pH ~3 with cold, aqueous 0.5N HCl and re-extracted with EtOAc. The combined organic layers are washed with brine, dried over anhydrous

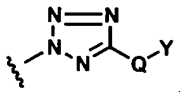
$MgSO_4$ and evaporated to dryness under vacuum. The crude reaction mixture contains at least four products; all of the products are isolated after flash chromatography on silica gel, using hexane/EtOAc (gradient from 9:1 to 3:1). The desired product **91d** is the least polar compound.

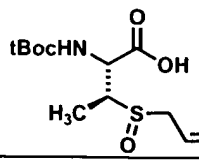
91D. A solution of compound **91d** in MeOH/H_2O (3:1) is mixed with aqueous NaOH (0.3 N) for 24 hours at RT and for 1 hour at 40°C. The reaction mixture is acidified with cold aqueous 0.5 N HCl, the MeOH is removed under vacuum and the remaining aqueous mixture is extracted with EtOAc. The organic phase is dried over $MgSO_4$ and evaporated to dryness in order to obtain compound **91e.** For further details of the preceding amino acid synthesis see WO 00/59929, which is herein incorporated by reference in its entirety.

91E. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using (2*S*, 3*S*)-*N*-Boc-2 amino-3(mercaptoallyl)butanoic acid **52e** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **91E** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 92. Compound of Formula II, wherein A = tBOC, G = OH, L = –S(O)–, W is  , Q = absent, Y = phenyl, j = 2, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

Formation of modified amino acid  **(92a).**

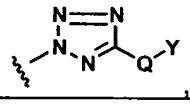
92A. The modified amino acid is prepared by dissolving sodium metaperiodate (1.1 eq.) in water and cooled to 0°C in an ice bath followed by adding dropwise a

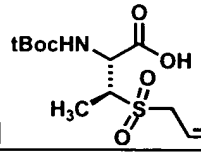
solution of compound **91d** in dioxane. The resulting reaction mixture is stirred for one hour at 0°C and 4 hours at 40°C. The reaction mixture is concentrated, water is added, and the mixture is extracted with methylene chloride twice. The combined organic layers are washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The methyl ester is then reduced via the method set forth in Example 91**D** to arrive upon the modified amino acid **92a**. For further details of the preceding amino acid synthesis may be found in T. Tsuda et al., *J. Am. Chem. Soc.*, **1980**, *102*, 6381-6384 and WO 00/59929, which are herein incorporated by reference in their entirety.

92B. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using the modified amino acid **92a** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **92B** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 93. Compound of Formula II, wherein A = tBOC, G = OH, L = $-S(O)_2-$, W is  , Q = absent, Y = phenyl, j = 2, m = s = 1, R^3 = methyl, and R^4 = H.

Formation of modified amino acid  (**93a**).

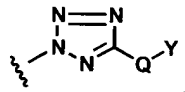
93A. The modified amino acid is prepared by dissolving sodium metaperiodate (1.1 eq.) in water and cooled to 0°C in an ice bath followed by adding dropwise a solution of compound **92d** in dioxane. The resulting reaction mixture is stirred for one hour at 0°C and 4 hours at 40°C. The reaction mixture is concentrated, water is added, and the mixture is extracted with methylene chloride twice. The combined organic layers are washed with water, brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The methyl ester is then reduced via the method set forth in Example 91**D** to

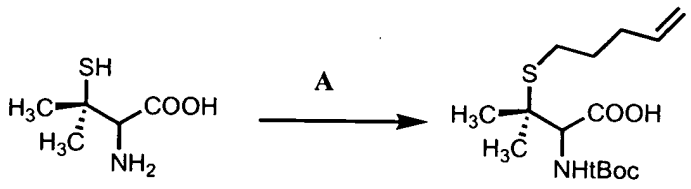
arrive upon the modified amino acid **92a**. For further details of the preceding amino acid synthesis may be found in T. Tsuda et al., *J. Am. Chem. Soc.*, **1980**, *102*, 6381-6384 and WO 00/59929, which are herein incorporated by reference in their entirety.

93B. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using the modified amino acid **93a** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **93B** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 94. Compound of Formula II, wherein A = tBOC, G = OH, L = $-SCH_2CH_2-$, W is  , Q = absent, Y = phenyl, j = 0, m = s = 1, and $R^3 = R^4 = CH_3$.



94a **94b**

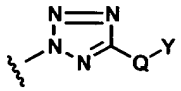
94A. Synthesis of (*S*)-N-Boc-2-amino-3-methyl-3(1-mercapto-4-butenyl)butanoic acid (**94b**)

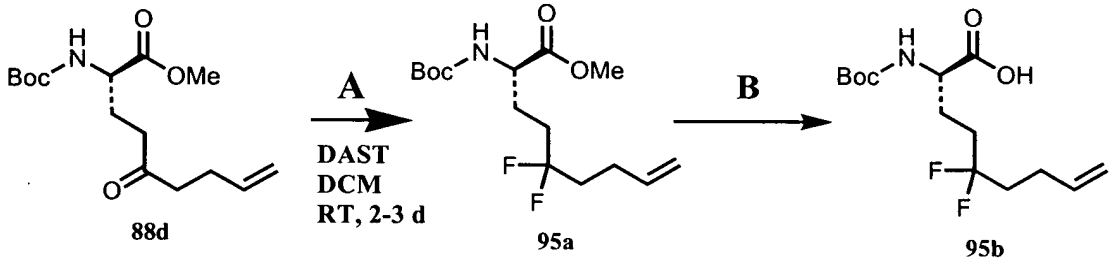
L-Penicillamine **94a** is dissolved in DMF/DMSO (5:1), subsequently, 4-bromopentene and $CsOH \bullet H_2O$ are added to the mixture and stirring is continued for an additional 12 hours. The DMF is subsequently removed *in vacuo*, the remaining mixture is diluted with 0.5 N HCl (at 0°C) to adjust the pH to ~4-5 and then extracted with 2 portions of EtOAc. The organic phase is washed with brine (2x), dried over $MgSO_4$ and evaporated to dryness to afford the crude carboxylic acid **94a**. For further details of the preceding amino acid synthesis see WO 00/59929, which is herein incorporated by reference in its entirety.

94B. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using the modified amino acid **94a** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **94B** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 95. Compound of Formula II, wherein A = tBOC, G = OH, L = $-CF_2CH_2-$, W is  , Q = absent, Y = phenyl, j = 1, m = s = 1, and $R^3 = R^4 =$ H.



Synthesis of (2*S*)-N-Boc-amino-5-difluoro-non-8-enoic acid (**95b**).

95A. To a solution of the ketone compound **88d** (0.30g, 1 mmol) in 5 ml DCM, DAST (Diethylaminosulfurtrifluoride, 0.2g, 1.2 eq) is added. The reaction is kept at RT over a period of 2-3 days. The solvent is evaporated and the residue is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as eluent (9:1→5:1→3:1→1:1), providing the isolated methyl ester **95a**. For further details concerning the preceding synthesis, see Tius, Marcus A et al., *Tetrahedron,* **1993**, *49, 16;* 3291-3304, which is herein incorporated by reference in its entirety.

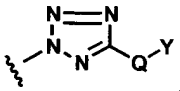
95B. Methyl ester **95a** is dissolved in THF/MeOH/H_2O (2:1:1) and LiOH•H_2O is added. The solution is stirred at RT for 2hours, and is then acidifies with 1N HCl to pH ~

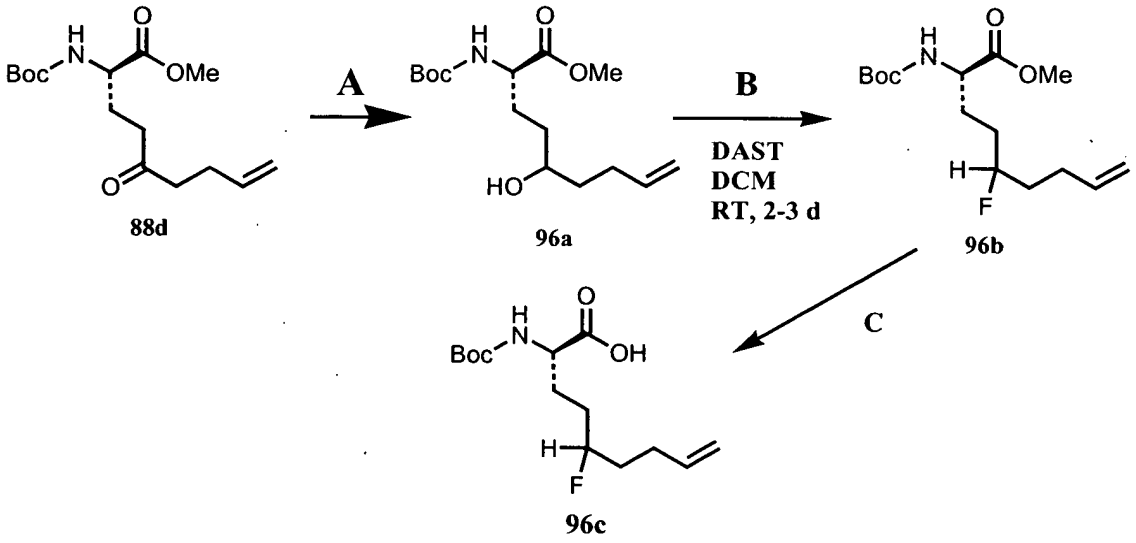
3 before the solvents are removed *in vacuo* to afford the crude (2*S*)-N-Boc-amino-5-difluoro-non-8-enoic acid **95b**.

95C. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using crude (2*S*)-N-Boc-amino-5-difluoro-non-8-enoic acid **95b** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **95C** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 96. Compound of Formula II, wherein A = tBOC, G = OH, L = –CFHCH$_2$–, W is  , Q = absent, Y = phenyl, j = 1, m = s = 1, and R^3 = R^4 = H.



Synthesis of (2*S*)-N-Boc-amino-5-fluoro-non-8-enoic acid (**96c**).

96A. To a solution of the ketone compound **88d** in 5 ml methanol, $NaBH_4$ (2.2 eq) is added. The reaction mixture is stirred at RT over a period of 2-6 hours, and then quenched by 1M ammonium chloride and extracted with EtOAc (30 ml). The solvent is evaporated and the crude hydroxy compound **96a** is obtained.

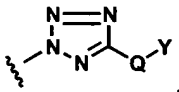
96B. The hydroxy compound **96a** is dissolved in 5 ml DCM to which DAST (0.2g, 1.2 eq) is added and stirred at –45 °C for 1 hour. The reaction mixture is then warmed to RT and stirred over a period of 2-3 days. The solvent is evaporated and the residue is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as eluent (9:1→5:1→3:1→1:1), providing the isolated monofluoro compound methyl ester **95b.** For further details concerning this synthesis see Buist, Peter H et al., *Tetrahedron Lett.*, **1987**, *28,* 3891-3894, which is herein incorporated by reference in its entirety.

96B. Methyl ester **96b** is dissolved in THF/MeOH/H_2O (2:1:1) and LiOH•H_2O is added. The solution is stirred at RT for 2hours, and is then acidifies with 1N HCl to pH ~ 3 before the solvents are removed *in vacuo* to afford the crude (2*S*)-N-Boc-amino-5-difluoro-non-8-enoic acid **96c**.

96C. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using crude (2*S*)-N-Boc-amino-5-monofluoro-non-8-enoic acid **96b** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **96C** and 5-phenyl-1H-tetrazole by the replacement method elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

Example 97. Compound of Formula III, wherein A = tBOC, G = OH, L = absent, W is  , Q = absent, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

97A. The saturated cyclic peptide precursor mesylate is prepared by catalytic reduction of the mesylate cyclic peptide precursor **2** with Pd/C in MeOH in the presence of H_2.

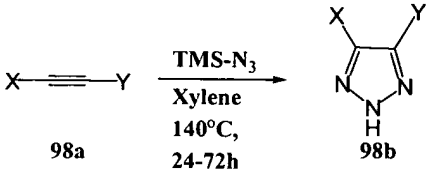
The title compound is prepared with the saturated cyclic peptide precursor mesylate formed in **97A** and 5-phenyl-1H-tetrazole by the replacement method

elucidated in Example 21 followed by hydrolysis of the ethyl ester via the method set forth in Example 22.

The compounds of the present invention exhibit potent inhibitory properties against the HCV NS3 protease. The following examples elucidate assays in which the compounds of the present invention were tested for anti-HCV effects.

Example 98. Triazole Synthesis

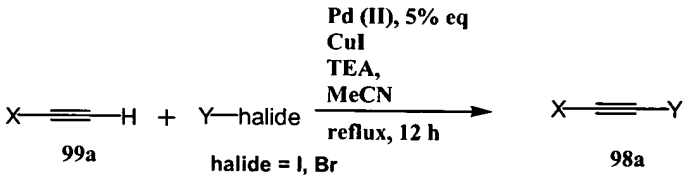
Exemplary triazole derivatives for use in preparing compounds of the invention may be prepared as set forth in the examples below:



Triazoles of the present invention may be prepared by reacting 4mmol of alkyne compound **98a**, which is commercially available or made from procedures elucidated *infra*, and 8mmol of trimethylsilyl azide in 2ml of xylenes in a pressure tube for 24-72 hours at 140°C. The resulting reaction mixture was directly separated by silica column, yielding triazole **98b** in 30-90% yield.

Example 99. Alykyne Synthesis

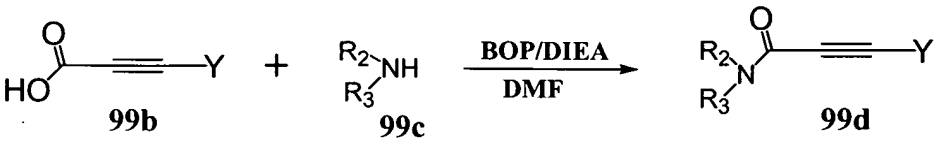
99A. Sonogashira Reaction



Alkynes used in the present invention can be made by the Sonogashira reaction by reaction of a degassed solution of 4mmol of primary alkyne compound **99a**, 4mmol of an aryl halide (Y–halide), and 1ml of triethylamine and 10ml of acetonitrile with 140mg(0.2mmol) of $PdCl_2(PPh_3)_2$ and 19mg(0.1mmol) of CuI. The resulting reaction mixture is degassed and stirred for 5 minutes at RT. The reaction is then heated to 90°C and stirred for 12 hours. Subsequently, the reaction mixture is concentrated *in*

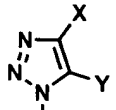
vacuo and purified by silica column to afford the substituted alkyne **98a** in a 60-90% yield.

99B. Synthesis of Alkynyl Amides

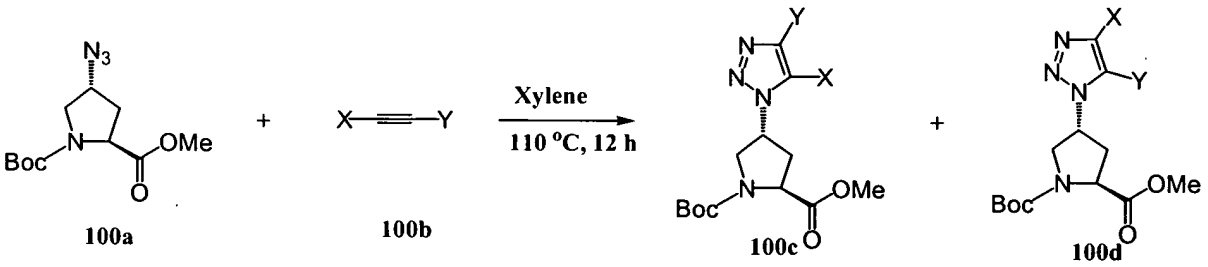


Additional alkynes used in the present invention can be made by reacting 10mmol of alkynyl acid **99b**, 11mmol of BOP, and 22mmol of DIEA in 15ml of DMF with 11mmol of amine **99b** and stirring at room temperature for 3 hours. The reaction mixture is then extracted by ethyl acetate (2x50ml); washed with 1M NaHCO3(2x30ml), water(2x30ml), 5% citric acid(2x50ml) and brine(2x30ml); dried over anhydrous sodium sulfate; and concentrated *in vacuo* to afford alkyne **99d** in a 90% yield.

Example 100. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = H, Y = 4-t-butylphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

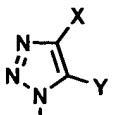


The title compound was prepared by the following method: 2mmol (0.54g) of Boc methyl ester azidoproline **100a** and 2.5mmol of 4-tert-Butylphenylacetylene **100b** were dissolved in 2ml of xylenes and stirred at 110°C for 12 hours. The resulting reaction mixture was directly separated by silica column to resolve isomers **100c** and **100d**, with a yield of 90%.

The title compound was then formed via the RCM procedure described in Example 1 using **100b** in the place of hydroxyl proline, followed by hydrolysis of the ethyl ester via the procedure described in Example 106.

$[M+Na]^+ = 671.72$.

Example 101. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

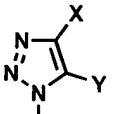


W is , X = 4-t-butylphenyl, Y = H, j = 3, m = s = 1, and $R^3 = R^4 = H$.

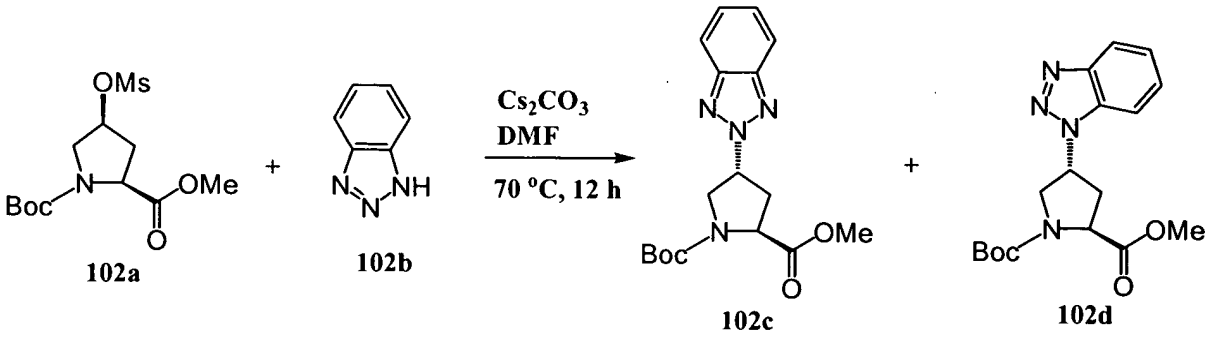
The title compound was prepared via RCM procedure described in Example 1 using **100c** in the place of hydroxyl proline, followed by hydrolysis of the ethyl ester via the procedure described in Example 106.

$[M+H]^+ = 649.44$.

Example 102. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X and Y are taken together = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

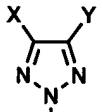


The triazole-substituted proline corresponding to the title compound was prepared by dissolving 1.5mmol(0.5g) of hydroxyproline mesylate **102a** and 4.5 mmol of benzotriazole **102b** in 5ml of DMF, adding 9mmol(2.9g) of cesium carbonate and stirring the resulting reaction mixture at 70°C for 12 hours. The reaction mixture was extracted with EtOAc, washed with 1M sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Expected isomers **102c** and **102d** were resolved via silica column chromatography.

The title compound was then formed via the RCM procedure described in Example 1 using **102d** in the place of hydroxyl proline, followed by hydrolysis of the ethyl ester via the procedure described in Example 106.

$[M+Na]^+ = 588.46$.

Example 103. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

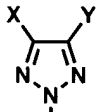


W is , X and Y taken together = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was formed via the RCM procedure described in Example 1 using **102c** in the place of hydroxyl proline, followed by hydrolysis of the ethyl ester via the procedure described in Example 106.

$[M+Na]^+ = 588.50$.

Example 104. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



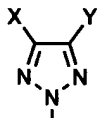
W is , X = Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The triazole-substituted proline corresponding to the title compound was prepared by dissolving 1.5mmol(0.5g) of hydroxyproline mesylate **102a** and 4.5 mmol of benzotriazole **102b** in 5ml of DMF, adding 9mmol(2.9g) of cesium carbonate and stirring the resulting reaction mixture at 70°C for 12 hours. The reaction mixture was extracted with EtOAc, washed with 1M sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*.

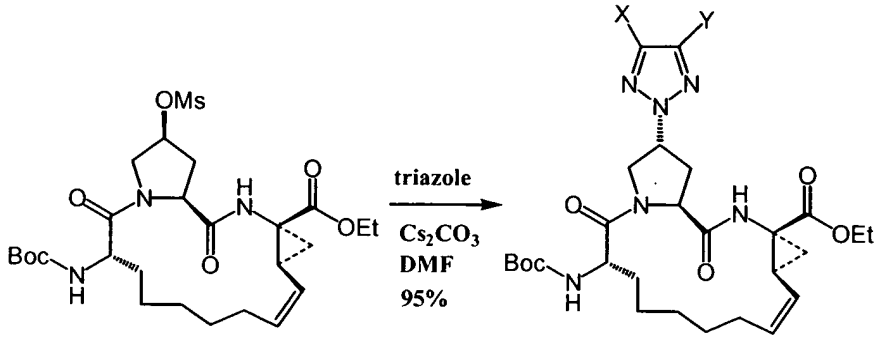
The title compound was then formed via the RCM procedure described in Example 1 using the triazole-substituted proline of the present example in the place of hydroxyl proline, followed by hydrolysis of the ethyl ester via the procedure described in Example 106.

$[M+Na]^+ = 690.42$.

Example 105. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent,



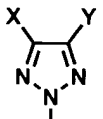
W is  , X = Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.



2 105

The title compound was prepared by dissolving 0.041mmol of the title compound of Example 2 and 0.123mmol of 4,5 -diphenyltriazole in 3ml of DMF, adding 0.246mmol of cesium carbonate (80mg), and reacting at 70°C for 12 hours. The reaction mixture was then extracted with EtOAc and washed with 1M sodium bicarbonate (2x30ml) and water (2x30ml). The resulting organic solution was concentrated *in vacuo* to dryness.

Example 106. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,

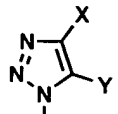


W is  , X = Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

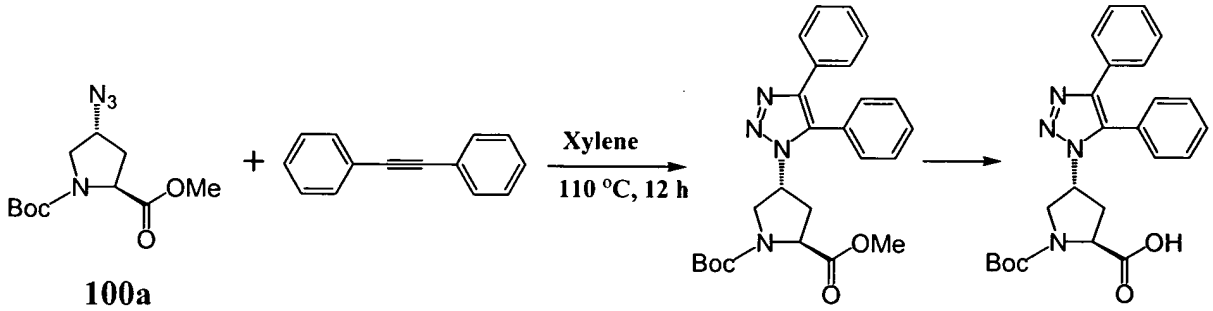
The title compound was prepared by dissolving 0.041mmol of the title compound of Example 105 in 3ml of dioxane, adding 2ml of 1M LiOH, and reacting at RT for 8 hours. Subsequently, the pH of reaction mixture was adjusted to 3 with citric acid, extracted with EtOAc, followed by washing with brine and water. The organic solution was concentrated *in vacuo* for purification by HPLC.

$[M+Na]^+ = 690.42$.

Example 107. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

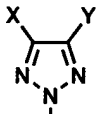


The triazole-substituted proline precursor of the title compound was prepared by dissolving 0.93mmol (0.25g) of azidoproline **100a** and 1mmol of diphenyl acetylene in 2ml of xylenes, heated to 110°C, and stirred for 12 hours. The reaction mixture was directly separated by silica column to afford 0.27g of **107a** (90%). [M+H]+: 449.05. 0.26g of **107b** was obtained by the hydrolysis procedure elucidated in Example 105 (99%).

The title compound was then formed via the RCM procedure described in Example 1 using **107b** in the place of hydroxyl proline.

$[M+Na]^+ = 691.99$.

Example 108. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = n-propyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

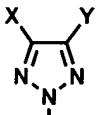
108a Triazole Formation

The 4-(n-propyl)-5-phenyltriazole was prepared via the procedure of Example 98 using n-propyl phenylacetylene and sodium azide.

The title compound was prepared with the title compound of Example 2 and 4-(n-propyl)-5-phenyltriazole **108a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+Na]^+$ = 657.99.

Example 109. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = m-methoxyphenyl Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

109a Alkyne Formation

The 2-(m-methoxyphenyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 9**9A** from 4-methoxyphenylacetylene and 3-bromoanisole.

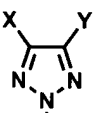
109b Triazole Formation

The 4-(m-methoxyphenyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using alkyne **109a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(m-methoxyphenyl)-5-(p-methoxyphenyl)triazole **109a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+Na]^+$ = 752.08.

Example 110. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = m-bromophenyl Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

110a Alkyne Formation

The 2-(m-bromophenyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 4-methoxyphenylacetylene and 3-iodo-5-bromobenzene.

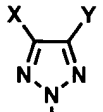
110b Triazole Formation

The 4-(m-bromophenyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using alkyne **110a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(m-bromophenyl)-5-(p-methoxyphenyl)triazole **110a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+Na]^+ = 800.05$.

Example 111. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = 1-napthyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

111a Alkyne Formation

The 2-(1-napthyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 1-iodonapthelene and 4-methoxyphenylacetylene.

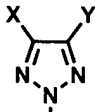
111b Triazole Formation

The 4-(m-bromophenyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(1-napthyl)-4-methoxyphenylacetylene **113a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(1-napthyl)-5-(p-methoxyphenyl)triazole **113a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+Na]^+ = 772.11$.

Example 112. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = 2-thienyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

112a Alkyne Formation

The 2-(2-thienyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 2-iodo-thiophene and 4-methoxyphenylacetylene.

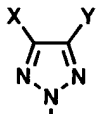
112b Triazole Formation

The 4-(2-thienyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(2-thienyl)-4-methoxyphenylacetylene **112a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(2-thienyl)-5-(p-methoxyphenyl)triazole **112a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 705.31$.

Example 113. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = 3-thienyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

113a Alkyne Formation

The 2-(3-thienyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99a from 2-iodo-thiophene and 4-methoxyphenylacetylene.

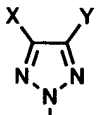
113b Triazole Formation

The 4-(3-thienyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(3-thienyl)-4-methoxyphenylacetylene **113a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(3-thienyl)-5-(p-methoxyphenyl)triazole **113a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+Na]^+ = 727.21$.

Example 114. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = 4-pyrazolyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

114a Alkyne Formation

The 2-(4-pyrazolyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 4-iodopyrazole and 4-methoxyphenylacetylene.

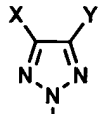
114b Triazole Formation

The 4-(4-pyrazolyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(4-pyrazolyl)-4-methoxyphenylacetylene **114a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(4-pyrazolyl)-5-(p-methoxyphenyl)triazole **114a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 700.82$.

Example 115. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = 3-pyridyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

115a Alkyne Formation

The 2-(3-pyridyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 3-iodopyridine and 4-methoxyphenylacetylene.

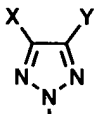
115b Triazole Formation

The 4-(3-pyridyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(3-pyridyl)-4-methoxyphenylacetylene **115a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(3-pyridyl)-5-(p-methoxyphenyl)triazole **115a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 700.36$.

Example 116. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = 2-pyridyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

116a Alkyne Formation

The 2-(2-pyridyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99A from 2-iodopyridine and 4-methoxyphenylacetylene.

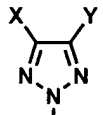
116b Triazole Formation

The 4-(2-pyridyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(2-pyridyl)-4-methoxyphenylacetylene **116a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(2-pyridyl)-5-(p-methoxyphenyl)triazole **116a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

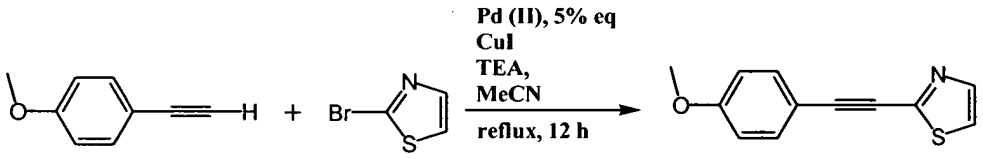
$[M+H]^+$ = 700.82.

Example 117. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = 2-thiazolyl, Y = p-methoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

A

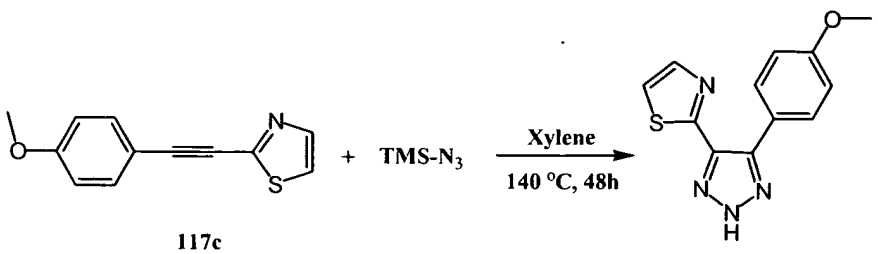


117a 117b 117c

117A. Alkyne Formation

The alkyne of the current example, 2-(2-thiazolyl)-4-methoxyphenylacetylene was prepared by adding to a degassed solution of 4mmol of 4-ethynylanisole, 4mmol of 2-bromothiazole, and 1ml of triethylamine in 10ml of acetonitrile,140mg(0.2mmol) of $PdCl_2(PPh_3)_2$ and 19mg(0.1mmol) of CuI. The mixture was degassed and stirred for 5 minutes at RT and heated to 90°C for 12 hours. The reaction mixture was concentrated *in vacuo* and purified by silica column to afford 0.61g of brown liquid in a 70% yield.

[M+H]+: 216.17, 1HNMR ($CDCl_3$, 500MHz) δ7.765(d, J=3Hz, 1H), 7.472~7.455(m, 2H), 7.277 (d, J=3.5Hz, 1H), 6.837~6.820 (m, 2H), 3.768 (s, 3H).

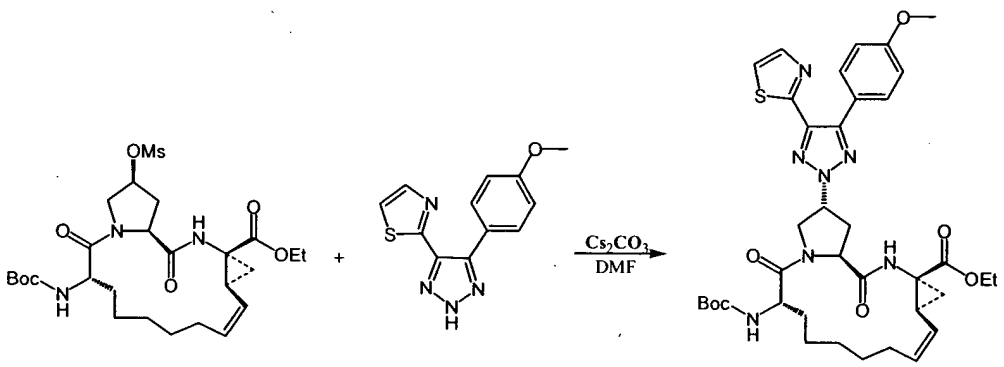


117c 117d

117B. Triazole Formation

The 4-(2-thiazolyl)-5-(p-methoxyphenyl) triazole **117d** was prepared by adding to a pressure tube 0.3g of **117c**, 0.74ml of trimethylsilyl azide, and 4ml of xylenes and heating the mixture to 140°C for 48 hours. The reaction mixture was directly separated by silica column to afford a brown liquid (**117d**) after purification (0.18g, 50%).

[M+H]+: 259.27, 1HNMR (DMSO-d_6), 500MHz) δ 8.016(d, J=8.5Hz, 2H), 7.929(d, J=3Hz, 1H), 7.817(d, J=3Hz, 1H), 7.066(d, J=8.5Hz, 2H), 3.824(s, 3H).

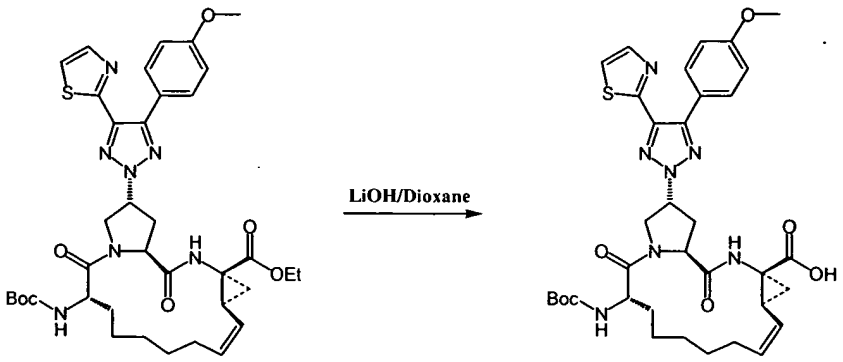


2 117d 117e

117c. Ethyl Ester **117e** was prepared by dissolving 0.041mmol of mesylate of macrocyclic precursor **117d** and 0.123mmol of **117d** in 3ml of DMF, adding 0.246mmol cesium carbonate, and reacting at 70°C for 12 hours. The reaction mixture was extracted with EtOAc, washed with 1M sodium bicarbonate (2x30ml) and water (2x30ml), and concentrated *in vacuo* to obtain ethyl ester **117e**.

[M+H]+: 734.34

Preparation of title compound

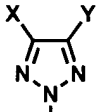


117e 117

Hydrolysis of ethyl ester **117c** was achieved by dissolving **117e** in 3ml of dioxane, adding 2ml of 1M LiOH, and stirring the resulting reaction mixture at RT for 8 hours. The pH of the reaction mixture was adjusted to 3 with citric acid; then the reaction mixture was extracted with EtOAc, and washed with brine and water. The organic solution was concentrated *in vacuo* for purification by HPLC which afforded a yellow powder after lyophilization (10mg, yield 34%).

[M+H]+: 706.33, 1HNMR (DMSO-d_6, 500MHz) δ 12.283 (s, broad, 1H), 8.750 (s, broad, 1H), 8.014 (d, J=9Hz, 2H), 7.938 (d, J=3.5Hz, 1H), 7.852 (d, J=3.5Hz, 1H), 6.997 (d, J=8Hz, 2H), 6.927 (d, J=7, 1H), 5.555 (s, broad, 1H), 5.499 (m, 1H), 5.298 (t, J=18Hz and 9Hz, 1H), 4.643 (t, J=16 Hz and 8Hz, 1H), 4.558 (d, J=11.5Hz, 1H), 4.125~4.093 (m, 2H), 3.802 (s, 3H), 2.890~2.847 (m, 1H), 2.542~2.497(m, 2H), 2.123~2.106 (m, 1H), 1.806(s, broad, 1H), 1.701~1.663(m, 1H), 1.519(s, broad, 1H), 1.460~1.435(m, 1H), 1.314~1.074(m, 16H).

Example 118. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = benzyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

118a Alkyne Formation

The 2-(benzyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 117A from 4-iodobenzene and 3-phenyl-propyne.

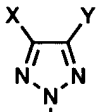
118b Triazole Formation

The 4-(benzyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(benzyl)-4-methoxyphenylacetylene **118a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(2-benzyl)-5-(p-methoxyphenyl)triazole **118a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 700.82$.

Example 119. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = n-butyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

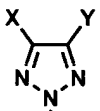
119a Triazole Formation

The 4-(n-butyl)-5-phenyl triazole was prepared via the procedure of Example 3 using n-butyl-1-phenylacetylene and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(n-butyl)-5-phenyl triazole **119a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 649.44$.

Example 120. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = n-propyl, Y = n-propyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

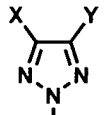
120a Triazole Formation

The 4,5-(n-propyl)triazole was prepared via the procedure of Example 3 using 4-octyne and sodium azide.

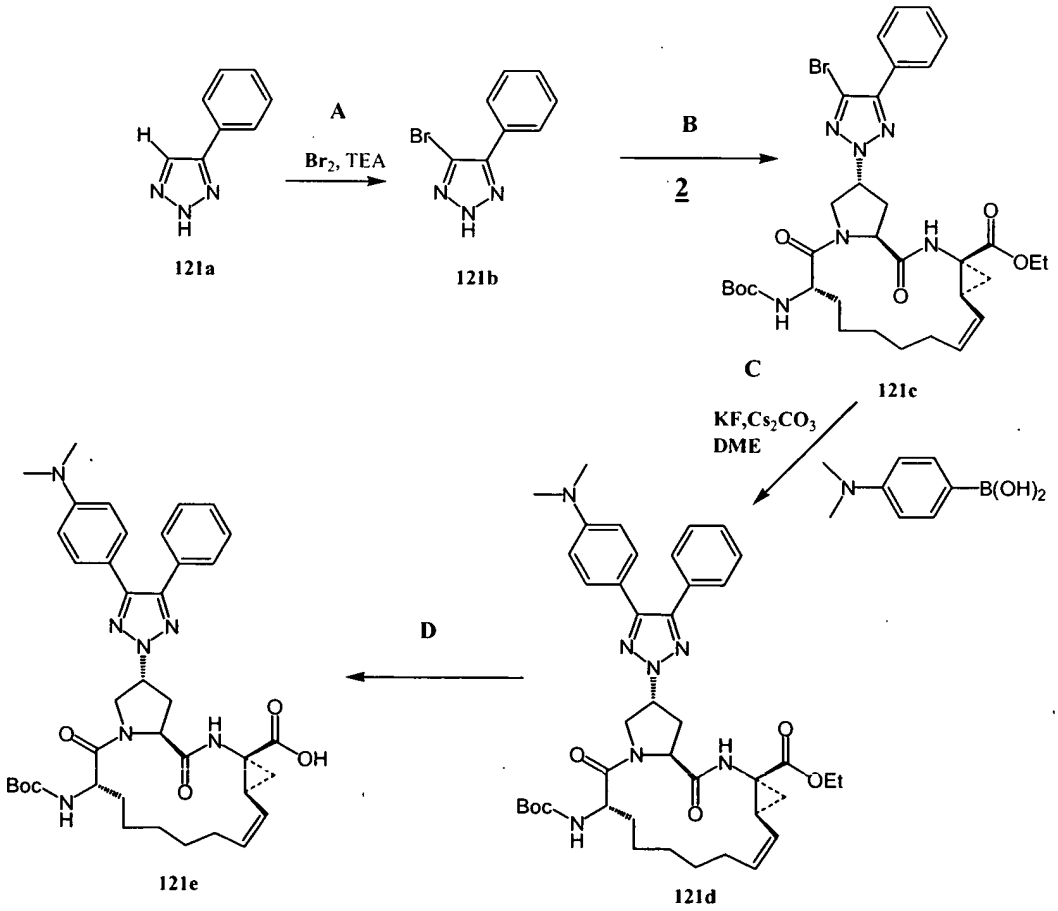
The title compound was prepared with the title compound of Example 2 and the 4,5-(n-propyl)triazole **120a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106

$[M+H]^+$ = 601.46.

Example 121. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is ~~~ , X = 4-(N,N-dimethylamino)phenyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4$ = H.



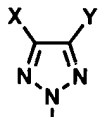
121A. Bromination. Bromo-substituted phenyl triazole **121b** was prepared by dissolving 1mmol of **121a** (Triazole **121a** was prepared by the method set forth in Example 2 using commercial phenyl acetylene and sodium azide) in 16ml 1:15 MeOH/$CHCl_3$, adding 0.28ml of TEA, and in a dropwise manner adding 0.128ml of bromine. The resulting reaction mixture was stirred for 2 hours. To the reaction mixture was added cold 10% $Na_2S_2O_5$ until the the mixture turned colorless. The mixture was extracted with EtOAc, washed with brine and water, dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.216g of **121b** after purification by silica column (97%). [M+H]+: 224.19.

121B. Mesylate replacement. 0.2g of **121c** was prepared via the procedure elucidated in Example 3 from purified **121b** and the title compound from Example 2. [M+Na]+: 721.00.

121C. Suzuki Coupling. Ethyl ester **121d** was prepared by dissolving 0.07mmol (50mg) of **121c** in 3ml of DME and adding to this solution 0.21mmol (35mg) of 4-dimethylaminophenyl boric acid, 137mg of cesium carbonate, and 100mg of KF. To the subsequently degassed reaction mixture was added 5mg of $Pd(PPh_3)_4$. The resulting reaction mixture was heated to 90°C and stirred for 12 hours. The reaction mixture then was extracted with EtOAc, washed with brine and water, dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica column to afford 40mg (78% yield) of **121d**.

121D. Ethyl Ester Hydrolysis. 12mg of **121e** was made via the procedure set forth in 106 from **121d** after purification by HPLC (30%). [M+H]+: 712.33.

Example 122. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = (N,N-diethylamino)methyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

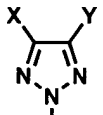
122a Triazole Formation

The 4-(N,N-diethylaminomethyl)-5-phenyltriazole was prepared via the procedure of Example 3 using 3-diethylamino-1-phenylpropyne and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(N,N-diethylaminomethyl)-5-phenyltriazole **122a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

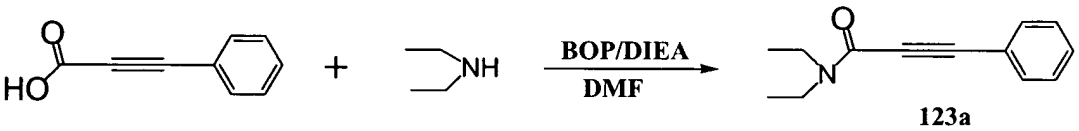
$[M+H]^+ = 678.44$.

Example 123. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = N,N-diethylaminocarbonyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 =$ H.

123A. Alkyne Formation



123a

Alkyne **123a** was prepared by dissolving 10mmol of phenylpropynoic acid, 11mmol of BOP, and 22mmol of DIEA in 15ml of DMF and to which was added 11mmol of diethylamine. The resulting reaction mixture was then stirred at RT for 3 hours. The reaction mixture was extracted with EtOAc (2x50ml), washed with 1M NaHCO3 (2x30ml), water (2x30ml), 5% citric acid (2x50ml), and brine (2x30ml). The organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 1.8g (90%) of **123a** [M+H]+: 202.09.

123B. Triazole Formation

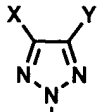
The 4-(N,N-diethylaminocarbonyl)-5-phenyltriazole **123b** was prepared via the procedure of Example 3 using **123a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(N,N-diethylaminocarbonyl)-5-phenyltriazole **123b** according to the procedure set

forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

[M+H]+: 692.47.

Example 124. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = m-chlorophenyl, Y = 4-ethoxyphenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

124a Alkyne Formation

The 2-(m-chlorophenyl)-4-methoxyphenylacetylene was prepared via the procedure of Example 99 from 3-chloro-bromobenzene and 4-methoxyphenylacetylene.

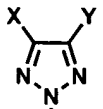
124b Triazole Formation

The 4-(m-chlorophenyl)-5-(p-methoxyphenyl)triazole was prepared via the procedure of Example 3 using 2-(m-chlorophenyl)-4-methoxyphenylacetylene **124a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(m-chlorophenyl)-5-(p-methoxyphenyl)triazole **124a** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

$[M+H]^+ = 747.37$.

Example 125. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , X = 2-phenylethenyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared with by the Suzuki reaction described in Example 121 from **121c** and phenylethenylboronic acid and subsequent hydrolysis by the procedure described in Example 106.

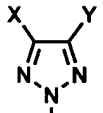
$[M+H]^+ = 695.30$.

Example 126. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, W is 5,6-methylbenzotriazole, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound was prepared with the title compound of Example 2 and the 5,6-methylbenzotriazole according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

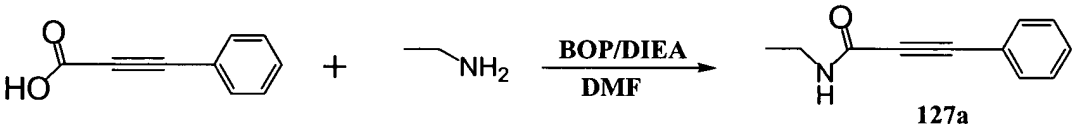
$[M+H]^+ = 595.42$.

Example 127. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is , X = N-ethylaminocarbonyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

127a. Alkyne Formation



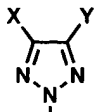
127a

Alkyne **127a** was prepared by dissolving 10mmol of phenylpropynoic acid, 11mmol of BOP, and 22mmol of DIEA in 15ml of DMF and to which was added 11mmol of ethylamine. The resulting reaction mizture was then stirred at RT for 3 hours. The reaction mixture was extracted with EtOAc (2x50ml), washed with 1M NaHCO3 (2x30ml), water (2x30ml), 5% citric acid (2x50ml), and brine (2x30ml). The organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 1.8g (90%) of **127a**. [M+H]+: 177.09.

127b Triazole Formation

The 4-(N-ethylaminocarbonyl)-5-phenyltriazole was prepared via the procedure of Example 3 using **127a** and sodium azide.

The title compound was prepared with the title compound of Example 2 and the 4-(N-ethylaminocarbonyl)-5-phenyltriazole **127b** according to the procedure set forth in Example 105 and subsequent hydrolysis of the ethyl ester via the procedure of Example 106.

Example 128. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  cyclopentyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

128a – Amine deprotection.

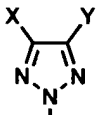
0.041mmol of the title compound of Example 105 is dissolved in 4ml of a 4M solution of HCl in dioxane and stirred for 1 hour. The reaction residue **128a** is concentrated *in vacuo*.

128b – Chloroformate Reagent

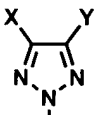
The chloroformate reagent **128b** is prepared by dissolving 0.045mmol of cyclopentanol in THF (3ml) and adding 0.09mmol of phosgene in toluene (20%). The resulting reaction mixture is stirred at room temperature for 2 hours and the solvent is removed *in vacuo*. To the residue is added DCM and subsequently concentrated to dryness twice *in vacuo* yielding chloroformate reagent **128b**.

128c – Carbamate formation

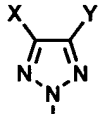
The title carbamate is prepared by dissolving residue **128a** in 1ml of THF, adding 0.045mmol of TEA, and cooling the resulting reaction mixture to 0°C. To this 0°C reaction mixture is added chloroformate reagent **128b** in 3ml of THF. The resulting reaction mixture is reacted for 2 hours at 0°C, extracted with EtOAc, washed by 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 106.

Example 129. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclobutyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

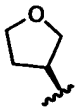
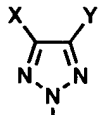
The title compound is prepared by the method described in Example 33 with the title compound of Example 105 and cyclobutanol, followed by ethyl ester hydrolysis by the procedure set forth in Example 106.

Example 130. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclohexyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

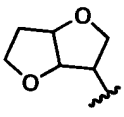
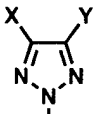
The title compound is prepared by the method in Example 33 with the title compound of Example 105 and cyclohexanol, followed by ethyl ester hydrolysis by the procedure set forth in Example 106.

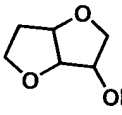
Example 131. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

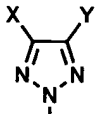
The title compound is prepared by the method described in Example 33 with the title compound of Example 105 and (R)-3-hydroxytetrahydrofuran, followed by ethyl ester hydrolysis by the procedure set forth in Example 106.

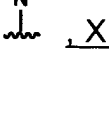
Example 132. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by the method in Example 33 with the title compound of Example 105 and (S)-3-hydroxytetrahydrofuran, followed by ethyl ester hydrolysis by the procedure set forth in Example 106.

Example 133. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, , W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

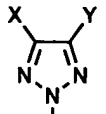
The title compound is prepared by the method in Example 33 with the title compound of Example 105 and  , followed by ethyl ester hydrolysis by the procedure set forth in Example 106.

Example 134. Compound of Formula II, wherein A = –(C=O)–R^1, wherein R^1 = 

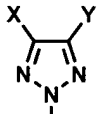
cyclopentyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 105 in 4ml of a 4M solution of HCl in dioxane and stirring the reaction mixture for 1 hour. The reaction residue is concentrated *in vacuo*. To this residue, 4ml of THF and 0.045mmol of TEA is added, the mixture is cooled to 0°C, to which is added 0.045mmol of the cyclopental acid chloride. The resulting reaction mixture is stirred for 2 hours at 0°C. The reaction mixture is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$ and concentrated to dryness *in*

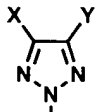
vacuo. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 106.

Example 135. Compound of Formula II, wherein A = –(C=O)–NH–R^1, wherein R^1  = cyclopentyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

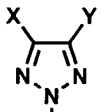
The title compound is prepared by dissolving 0.041mmol of the title compound from Example 105 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 106.

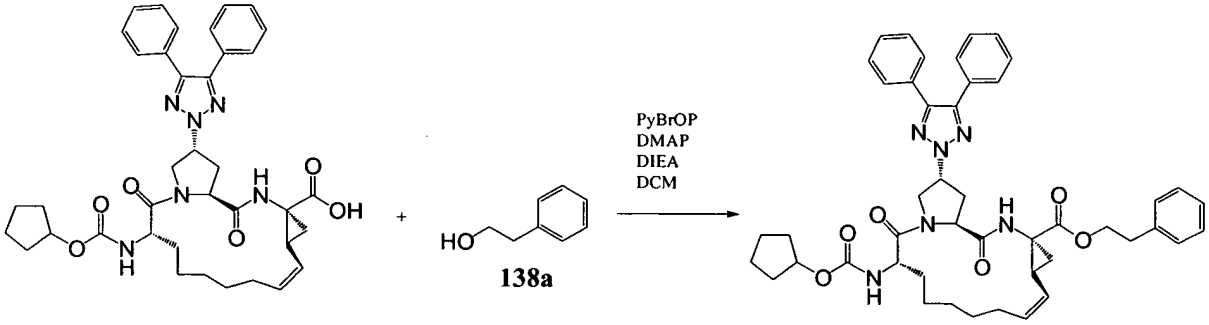
Example 136. Compound of Formula II, wherein A = –(C=S)–NH–R^1, wherein R^1  = cyclopentyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R^3 = R^4 = H.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 105 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isothiocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 106.

Example 137. Compound of Formula II, wherein A = $-S(O)_2-R^1$, wherein R^1 =  cyclopentyl, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

The title compound is prepared by dissolving 0.041mmol of the title compound from Example 105 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. To the resulting concentrated reaction residue, which has been dissolved in 4ml THF, is added 0.045mmol of TEA, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl solfonyl chloride and the resulting reaction mixture is stirred at 0°C for 2 hours. The solution is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 106.

Example 138. Compound of Formula II, wherein A = $-(C=O)-O-R^1$, R^1 =  cyclopentyl, G = –O–phenethyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.

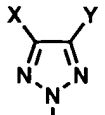


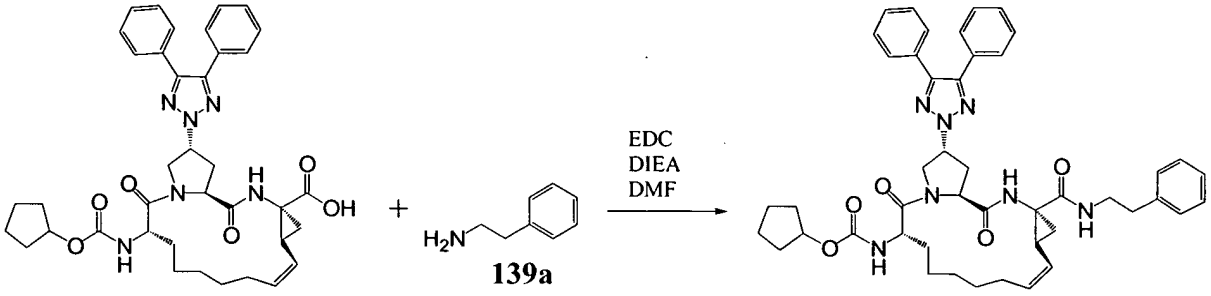
128 **138a** **138b**

The title compound is prepared by adding to a solution of the title compound of Example **128** and phenethyl alcohol **138a** in 0.5 ml DCM, is added 1.2 eq. PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at 0°C. The resulting reaction mixture is stirred for 1 hour at 0°C and then warmed to RT over a period of 4-12 hours. The

reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated phenethyl ester 138b.

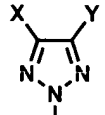
Other esters can be made using the same procedures.

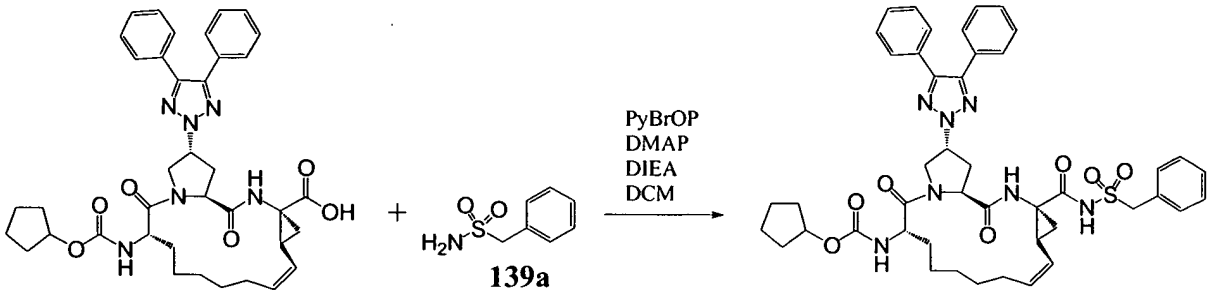
Example 139. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –NH–phenethyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.



128 **139a** **139b**

The title compound is prepared by adding to a solution of the title compound of Example **128** and phenethylamine **139a** (0.05 ml) in 0.5 ml DMF, EDC (1.2 eq.) and DIEA (4eq.) at 0°C. The resulting reaction mixture is stirred at 1 hour. Subsequently, the reaction is warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford title compound phenethyl amide **139b**. Other amides can be made using the same procedures.

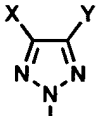
Example 140. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –$NHS(O)_2$–phenethyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and R3 = R4 = H.

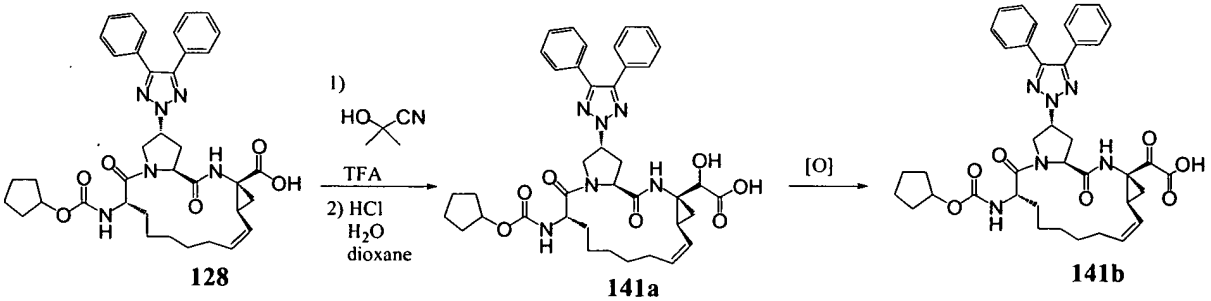


128 + 139a → 139b

The title compound is prepared by adding to a solution of the title compound of Example **128** and α-toluenesulfonamide **140a** (10mg) in 0.5 ml DCM, is added 1.2 eq. PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at 0°C. The resulting reaction mixture is stirred for 1 hour and then allowed to warm to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound sulfonamide **140b**.

Other sulfonamides can be made using the same procedure.

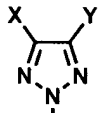
Example 141. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and and $R^3 = R^4 = H$.



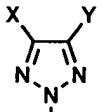
128 → 141a → 141b

The title compound is prepared by adding to a solution of the title compound of Example **128** in 0.5 ml THF, is added α-hydroxy-α-methyl-propionitrile (0.1 ml) and catalytic amount TFA at 0°C. The resulting reaction mixture is warmed from 0°C to RT over a period of 4-12 h followed by hydrolysis with concentrated hydrochloric acid in dioxane.

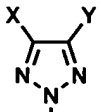
The reaction is then extracted with EtOAc, and washed with water and brine to yield α-hydroxy compound **141a** in its crude form. The crude compound **46b** undergoes a Dess-Martin oxidation in THF (0.5 ml), providing the α-carbonyl compound **46b** in crude form. The crude **141b** is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated keto acid **141c**.

Example 142. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = 
cyclopentyl, G = –(C=O)–O–phenethyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and and R^3 = R^4 = H.

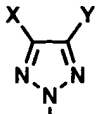
The title compound is prepared with the title compound keto acid of Example 141 and phenethanol according to the procedure set forth in Example 138.

Example 143. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = 
cyclopentyl, G = –(C=O)–NH–phenethyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and and R^3 = R^4 = H.

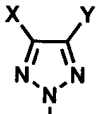
The title compound is prepared with the title compound keto acid of Example 141 and phenethyl amine according to the procedure set forth in Example 139.

Example 144. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = 
cyclopentyl, G = –(C=O)–NH–$S(O)_2$–benzyl, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and and R^3 = R^4 = H.

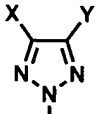
The title compound is prepared with the title compound keto acid of Example 141 and α-toluenesulfonamide according to the procedure set forth in Example 140.

Example 145. Compound of Formula II, wherein A = tBOC, G = OH, L = –(C=O)CH_2–, W is  , X = phenyl, Y = phenyl, j = 1, m = s = 1, and R^3 = R^4 = H.

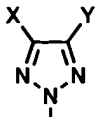
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 88C** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 146. Compound of Formula II, wherein A = tBOC, G = OH, L = –$CH(CH_3)CH_2$–, W is  , X = phenyl, Y = phenyl, j = 1, m = s = 1, R^3 = methyl, and R^4 = H.

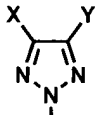
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 89G** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 147. Compound of Formula II, wherein A = tBOC, G = OH, L = –O–, W is  , X = phenyl, Y = phenyl, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

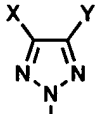
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 90D** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 148. Compound of Formula II, wherein A = tBOC, G = OH, L = –S–, W is  , X = phenyl, Y = phenyl, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

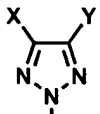
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 91E** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

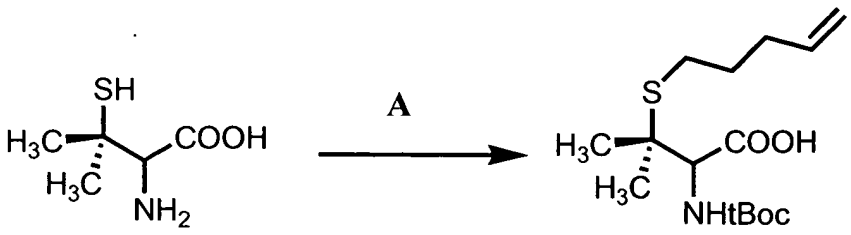
Example 149. Compound of Formula II, wherein A = tBOC, G = OH, L = –S(O)–,  W is , X = phenyl, Y = phenyl, j = 2, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 92B** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 150. Compound of Formula II, wherein A = tBOC, G = OH, L = $–S(O)_2–$,  W is , X = phenyl, Y = phenyl, j = 2, m = s = 1, R^3 = methyl, and R^4 = H.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 93B** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 151. Compound of Formula II, wherein A = tBOC, G = OH, L =  $–SCH_2CH_2–$, W is , X = phenyl, Y = phenyl, j = 0, m = s = 1, and $R^3 = R^4 = CH_3$.



151a 151b

151A. Synthesis of (*S*)-N-Boc-2-amino-3-methyl-3(1-mercapto-4-butenyl)butanoic acid (**151b**)

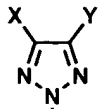
L-Penicillamine **151a** is dissolved in DMF/DMSO (5:1), subsequently, 4-bromopentene and $CsOH•H_2O$ are added to the mixture and stirring is continued for an additional 12 hours. The DMF is subsequently removed *in vacuo*, the remaining mixture is diluted with 0.5 N HCl (at 0°C) to adjust the pH to ~4-5 and then extracted with 2 portions of EtOAc. The organic phase is washed with brine (2x), dried over $MgSO_4$ and evaporated to dryness to afford the crude carboxylic acid **151a**.

151B. Synthesis of modified cyclic peptide precursor mesylate

The modified cyclic peptide precursor mesylate is prepared using the synthetic route detailed in Example 1 using the modified amino acid **151a** in place of Boc-L-2-amino-8-nonenoic acid **1a** followed by conversion to the corresponding mesylate via the method described in Example 2.

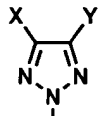
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **151B** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 152. Compound of Formula II, wherein A = tBOC, G = OH, L = CF_2CH_2,

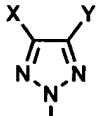


W is , X = phenyl, Y = phenyl, j = 1, m = s = 1, and $R^3 = R^4 = H$.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 95C** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 153. Compound of Formula II, wherein A = tBOC, G = OH, L = –$CHFCH_2$–, W is  , X = phenyl, Y = phenyl, j = 1, m = s = 1, and $R^3 = R^4 = H$.

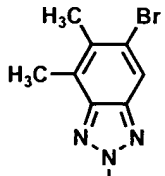
The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **Example 96C** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 154. Compound of Formula III, wherein A = tBOC, G = OH, L = absent, W is  , X = phenyl, Y = phenyl, j = 3, m = s = 1, and $R^3 = R^4 = H$.

154A. The saturated cyclic peptide precursor mesylate is prepared by catalytic reduction of the mesylate cyclic peptide precursor **2** with Pd/C in MeOH in the presence of H_2.

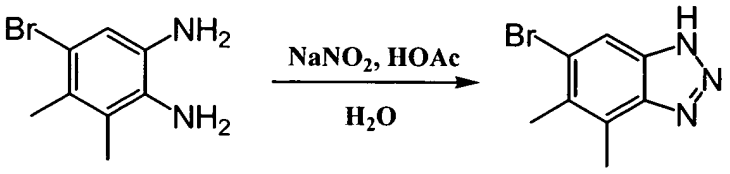
The title compound is prepared with the saturated cyclic peptide precursor mesylate formed in **154A** and 4,5 -diphenyltriazole by the replacement method elucidated in Example 105 followed by hydrolysis of the ethyl ester via the method set forth in Example 106.

Example 155. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , j = 3, m = s = 1, and $R^3 = R^4 = H$.

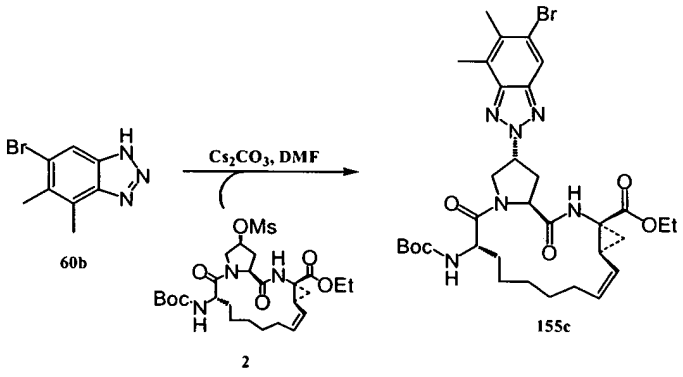
155A. Substituted benzotriazole formation



155a **155b**

The bromo-substituted benzotriazole **155b** of the present Example is prepared by combining 2.15g (10mmol) of 5-bromo-3, 4-dimethylbenzene-1,2-diamine, 1.15ml (20mmol) of glacial acetic acid, and 10ml of water and heating the resulting mixture to obtain a clear solution. The clear solution is then cooled to 5°C, a cold solution of 0.83g (12mmol) of sodium nitrite in 5ml of water is added, and the reaction mixture is heated to 70~80°C for 2 hours. The reaction mixture is then extracted with EtOAc, washed by brine and water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product is purified by silica column.

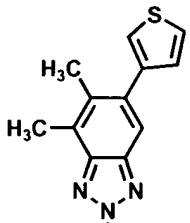
155B. Replacement



The ethyl ester **155c** is prepared by the replacement method described in Example 105 with the title compound of Example 2 and bromo-substituted benzotriazole **155b**.

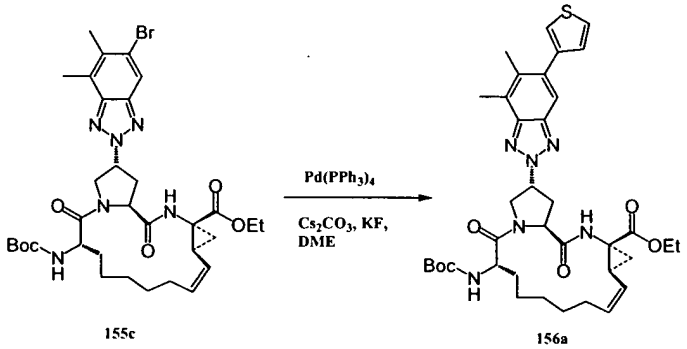
The title compound is ultimately prepared with ethyl ester **155c** by the hydrolysis procedure set forth in Example 106.

Example 156. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , j = 3, m = s = 1, and $R^3 = R^4 = H$.

156A. Suzuki Reaction

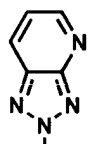


Compound **156a** of the present Example is prepared via a Suzuki coupling reaction with **155c** and 3-thienyl boronic acid as described in Example 26C.

156B. Hydrolysis

The title compound is prepared with ethyl ester **156a** by the hydrolysis procedure set forth in Example 106.

Example 157. Compound of Formula II, wherein A = tBOC, G = OH, L = absent,



W is  , j = 3, m = s = 1, and $R^3 = R^4 = H$.

157a. Bicyclic Compound Formation

The bicyclic compound of the present invention is prepared with 2,3-di aminopyridine by the procedure set forth in Example 157A.

The title compound is prepared with the bicyclic compound prepared in **157a** and the title compound of Example 2 by the replacement method described in Example 105, followed by hydrolysis of the ethyl ester via the procedure set forth in Example 106.

Example 158. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = Y = bromo, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

To a mixture of macrocyclic compound **1** (185 mg, 0.38 mmol), 4,5-dibromo-2H-pyridazin-3-one (95 mg, 0.38 mmol) and triphenylphosphine (197 mg, 0.75 mmol) in THF (5 mL) is added DIAD (148 μL, 0.75 mmol) dropwise at 0°C. After stirring at 0°C for 15 min., the solution is warmed to room temperature and is further stirred for 16 hours. The mixture is then concentrated *in vacuo* and the residue is purified by column chromatography eluting with 40% ethyl acetate-hexane to give 235 mg (86%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.8 (s, 1H), 7.1 (brs, 1H), 5.5 (m, 2H), 5.2 (m, 2H), 5.0 (m, 1H), 4.4 (brt, 1H), 4.0-4.2 (m, 4H), 2.9 (m, 1H), 2.6 (m, 1H), 1.8-2.3 (m, 5H), 1.4 (s, 9H), 1.2 (t, 3H). $[M+H]^+$ = 730.6.

Example 159. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

A mixture of the title compound of Example 162 (40 mg, 0.055 mmol), 3-thiophene boronic acid (35mg, 0.28 mmol), cesium carbonate (71 mg, 0.22 mmol), potassium fluoride monohydrate (41 mg, 0.44 mmol) is placed in a round bottom flask and is flushed twice with nitrogen. To this mixture is added DME and the resulting solution is flushed again with nitrogen before palladium tetrakis(triphenylphopshine) (7 mg, 10 mol%) is added. After flushing two more times with nitrogen, the mixture is heated to reflux for 20 hours. The mixture is then cooled and then diluted with water and extracted three times with EtOAc. The combined EtOAc layers are washed once

with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by column chromatography eluting with 20-40% EtOAc-hexane to give the title compound as a clear film (24 mg, 60%).

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.9 (s, 1H), 7.6 (s, 1H), 7.3 (s, 1H), 7.3 (m, 1H), 7.0 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 5.7 (m, 1H), 5.5 (m, 1H), 5.4 (brd, 1H), 5.2 (t, 1H), 5.0 (m, 1H), 4.6 (brt, 1H), 4.0-4.2 (m, 4H), 2.9 (m, 1H), 2.6 (m, 1H), 2.0-2.3 (m, 5H), 1.4 (s, 9H), 1.2 (t, 3H). $[M+Na]^+$ = 758.63.

Example 160. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

To a solution of the title compound in Example 2 (24 mg, 0.033 mmol) in THF/MeOH/H_2O (2/1/0.5 mL) is added lithium hydroxide (14 mg, 0.33 mmol). After stirring for 16 hours at room temperature, the mixture is acidified to pH 4 with citric acid and extracted three times with EtOAc. The combined organic extracts are washed once with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue is purified by column chromatography eluting with 5-10% methanol-chloroform to give the title compound (13 mg, 56%).

$[M+H]^+$ = 708.3.

Example 161. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = phenyl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by a double Suzuki coupling with phenylboronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+$ = 696.40

Example 162. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = 4-(N,N-dimethylamino)phenyl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by a double Suzuki coupling with 4-(N,N-dimethylamino)phenyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+$ = 782.30

Example 163. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = 4-(trifluoromethoxy)phenyl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by a double Suzuki coupling with 4-(trifluoromethoxy)phenyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+$ = 864.09

Example 164. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = 4-(methanesulfonyl)phenyl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by a double Suzuki coupling with 4-(methanesulfonyl)phenyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

Example 165. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = 4-(cyano)phenyl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by a double Suzuki coupling using 4-cyanophenyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+ = 746.14$

Example 166. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = pyrid-3-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared by a double Suzuki coupling using 3-pyridyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+ = 698.3$.

Example 167. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = 4-(morpholin-4-yl-methanonyl)phenyl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared by a double Suzuki coupling using 4-carboxyphenyl boronic acid and the title compound of Example 158 according to the procedure set forth in Example 159, followed by amide formation with morpholine, under standard amide bond formation conditions, e.g. PyBrOP, DIEA, and DMAP in DMF. The ethyl ester of the resulting compound is then hydrolyzed via the hydrolysis procedure of Example 160.

Example 168. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = bromo, Y = methoxy, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared from the title compound in Example 158 via hydrolysis of the ethyl ester according to the procedure described in Example 160, however addition of methoxy to the 5 position is observed in addition to hydrolysis of the ethyl ester.

$[M+H]^+$ = 652.2, 654.2.

Example 169. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X and Y taken together = phenyl, Z = 4-methoxyphenyl, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared according to the Mitsunobu conditions set forth in Scheme 20 with commercially available 4-(4-methoxy-phenyl)-2H-phthalazin-1-one, and subsequent hydrolysis of the ethyl ester via the procedure of Example 160.

$[M+H]^+$ = 700.1.

Example 170. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X and Y taken together = phenyl, Z = 4-chlorophenyl, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared according to the Mitsunobu conditions set forth in Scheme 20 with commercially available 4-(4-chloro-phenyl)-2H-phthalazin-1-one, and subsequent hydrolysis of the ethyl ester via the procedure of Example 160.

$[M+H]^+$ = 704.2.

Example 171. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = 4-fluorophenyl, Y = hydrogen, Z = phenyl, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared according to the Mitsunobu conditions set forth in Scheme 20 with commercially available 4-(4-fluoro-phenyl)-6-phenyl-2H-pyridazin-3-one, and subsequent hydrolysis of the ethyl ester via the procedure of Example 160.

$[M+H]^+$ = 704.2.

Example 172. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = hydrogen, Y = 1-piperidyl, Z = phenyl, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared according to the Mitsunobu conditions set forth in Scheme 20 with commercially available 6-phenyl-5-piperidin-1-yl-2H-pyridazin-3-one, and subsequent hydrolysis of the ethyl ester via the procedure of Example 160.

$[M+H]^+$ = 702.3.

Example 173. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = hydrogen, Y = bromo, Z = phenyl, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared according to the Mitsunobu conditions set forth in Scheme 20 with commercially available 5-Bromo-6-phenyl-2H-pyridazin-3-one.

$[M+H]^+$ = 726.3, 728.3.

Example 174. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = hydrogen, Y = thiophen-3-yl, Z = phenyl, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the title compound of Example 173 and thiophen-3-yl boronic acid according to the Suzuki coupling conditions described in Example 159, followed by the hydrolysis of the ethyl ester via the method described in Example 160.

$[M+H]^+$ = 730.3

Example 175. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = bromo, Y = 1-pyrrolidyl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

A mixture of the title compound in Example 158 (45 mg, 0.062 mmol), pyrrolidine (21 mL, 0.25 mmol), and potassium carbonate (34 mg, 0.25 mmol) in 2 mL of

acetonitrile is heated to reflux for 3 hours. After cooling to room temperature, the mixture is filtered through a sinter glass funnel and the filtrate is concentrated *in vacuo*. The residue is re-dissolved in ethyl acetate and then washed once with saturated sodium carbonate, once with brine, dried (MgSO4), filtered, and concentrated under vacuum to give a yellow residue which is chromatographed over silica gel eluting with 3% methanol-chloroform to give 37 mg (83%) of the title compound.

$[M+H]^+$ = 719.2, 721.2.

Example 176. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = thiophen-3-yl, Y = 1-pyrrolidyl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the title compound in Example 175 and thiephen-3-yl boronic acid using the Suzuki conditions described in Example 159, followed by hydrolysis of the ethyl ester according to the method set forth in Example 160.

$[M+H]^+$ = 694.3.

Example 177. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = bromo, Y = azido, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

A mixture of the title compound in Example 158 (45 mg, 0.062 mmol), sodium azide (16mg, 0.25 mmol), and potassium carbonate (34 mg, 0.25 mmol) in 2 mL of acetonitrile is heated to reflux for 3 hours. After cooling to room temperature, the mixture is filtered through a sinter glass funnel and the filtrate is concentrated *in vacuo*. The residue is re-dissolved in ethyl acetate and then washed once with saturated sodium carbonate, once with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum to give a yellow residue which is chromatographed over silica gel eluting with 3% methanol-chloroform to give 37 mg (83%) of the title compound.

Example 178. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = thiophen-3-yl, Y = azido, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the title compound in Example 177 and thiophen-3-yl boronic acid using the Suzuki conditions described in Example 159.

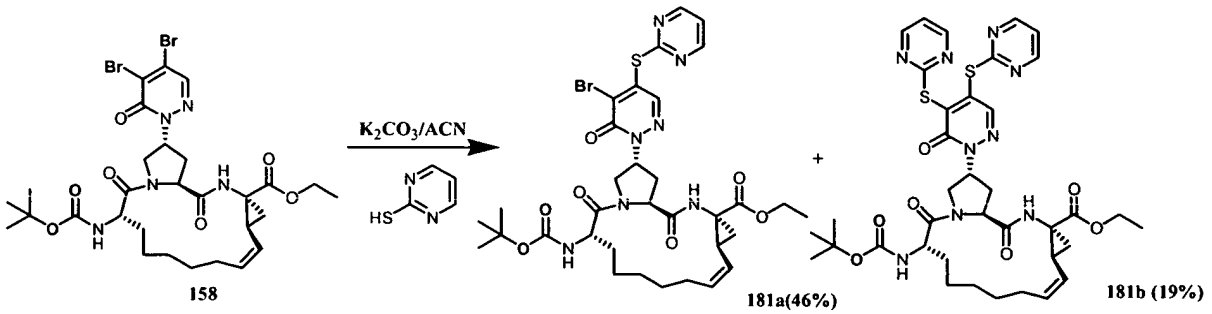
Example 179. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = thiophen-3-yl, Y = azido, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared by hydrolysis of the ethyl ester of the title compound of Example 178 via the hydrolysis procedure of Example 160.

Example 180. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = thiophen-3-yl, Y = tetrazol-2-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

To a solution of the title compound of Example 178 (2.63 mmol) in toluene (8 ml) is added KCN (10.53 mmol) and Et_3N•HCl (10.53 mmol). The mixture is heated at 115 °C for 18 hrs, diluted with DCM, washed with 5% citric acid (aq), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the ethyl ester of the title compound in crude form. Hydrolysis of the ethyl ester via the method described in Example 160 yields the title compound.

Example 181. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = mercapto–2–pryrimidine, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.



A mixture of the title compound in Example 158 (45 mg, 0.062 mmol), pyrimidine-2-thiol (0.25 mmol), and potassium carbonate (34 mg, 0.25 mmol) in 2 mL of

acetonitrile is heated to reflux for 3 hours. After cooling to room temperature, the mixture is filtered through a sinter glass funnel and the filtrate is concentrated *in vacuo*. The residue is re-dissolved in ethyl acetate and then washed once with saturated sodium carbonate, once with brine, dried (MgSO4), filtered, and concentrated under vacuum to give a yellow residue which is chromatographed over silica gel eluting with 3% methanol-chloroform to afford **181b** in a 19% yield. The ethyl ester of compound **181b** is then hydrolyzed via the method described in Example 160 to give the title compound.

$[M+H]^+ = 764.3$.

Example 182. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = bromo, Y = mercapto–2–pryrimidine, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4 =$ hydrogen.

The title compound is prepared by hydrolysis of the ethyl ester of compound **181a,** formed in Example 181, via the method set forth in Example 160.

$[M+H]^+ = 732.2, 734.2$.

Example 183. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = thiophen-3-yl, Y = mercapto–2–pryrimidine, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with compound **181a** from Example 181 and thiophen-3-yl boronic acid according to the Suzuki coupling conditions set forth in Example 159, followed by hydrolysis of the ethyl ester via the method described in Example 160.

Example 184. Compound of Formula II, wherein A = tBOC, G = OEt, L = absent, X = Y = thiazol-2-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

To a degassed solution of the title compound of Example 158 (1 mmol) and thiazol-2-yl stannane (2 mmol) is added $Pd(PPh_3)_4$ (10 mol%). The mixture is degassed

with nitrogen 2 more times and is heated to 100 °C for 3 hour. The cooled mixture is concentrated under vacuum and the residue is purified by column chromatography eluting with 30% EtOAc/Hexane followed by the hydrolysis of the ethyl ester via the method of Example 160 to give the title compound.

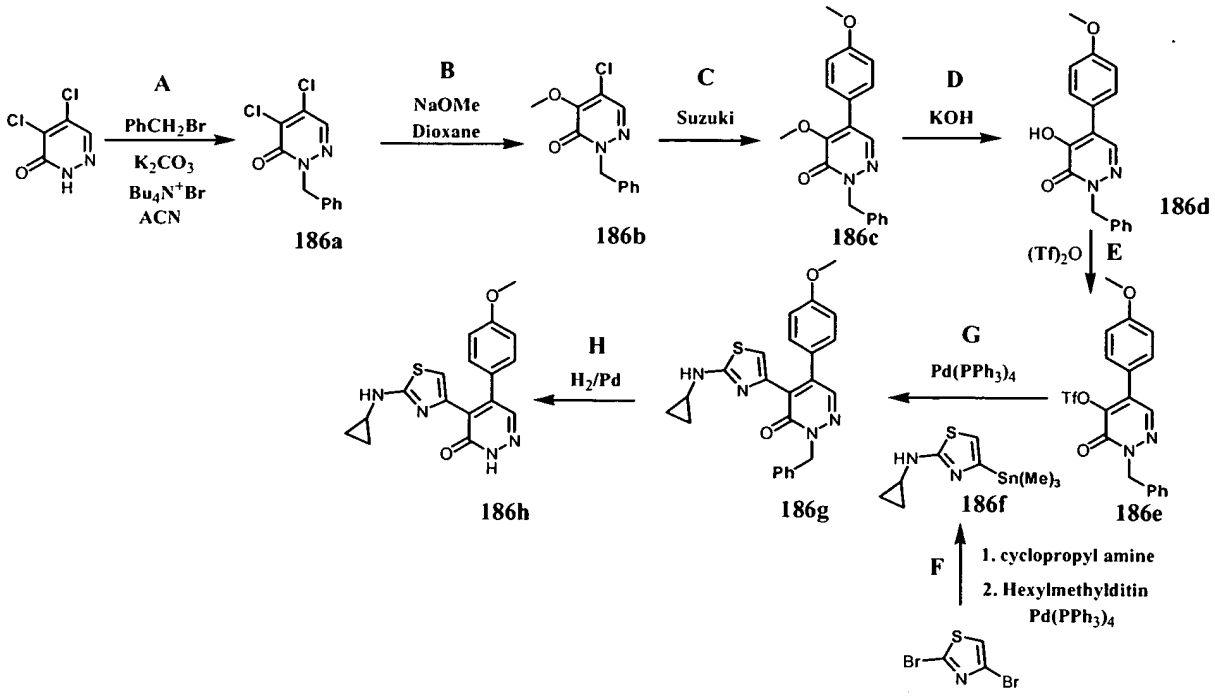
$[M+H]^+ = 710.3$.

Example 185. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = Y = imidazol-1-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared by adding to a dry mixture of the title compound from Example 158 (0.068 mmol), imidazole (2 eq.), Cs_2CO_3 (3 eq.), Xantphos (30 mol %), and $Pd(OAc)_2$ under nitrogen dioxane. The reaction mixture is then degassed and stirred at 75°C for 18 hours. Upon completion of the reaction, monitored via TLC, the reaction mixture is diluted with DCM, filtered, and concentrated *in vacuo*. The reaction mixture is then purified via silica column chromatography with 5% MeOH/$CHCl_3$ to afford the ethyl ester of the title compound. The ethyl ester is then hydrolyzed by the conditions set forth in Example 160 to afford the title compound.

Example 186. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X = 2-(cyclopropylamino)-thiazol-4-yl, Y = 4-methoxyphenyl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

Formation of 4-(2-Cyclopropylamino-thiazol-4-yl)-5-(4-methoxy-phenyl)-2H-pyridazin-3-one **(186h)**



186A. A mixture of commercially available 4,5-dichloropyridazin3(2*H*)-one (18 mmol), benzyl bromide (19 mmol), potassium carbonate (45 mmol), tetrabutylammonium bromide (1 mmol) and acetonitrile (45 mL) is stirred and heated under reflux for 1h. After cooling, the solvent is evaporated under reduced pressure. The residue is purified by filtration on a small silica gel column eluting with 10% EtOAc/Hexane to give compound **186a** as a white powder (81%). $[M+H]^+$ = 256.3.

186B. To a magnetically stirred solution of **186a** (4.5 mmol) in dry dioxane (20 mL) is added 1.0 mL of 21 wt% solution of sodium methoxide at room temperature. After 1 hour, the mixture is poured into water/ethyl acetate and the organic layer is dried over $MgSO_4$ and concentrated to an oil. The oil residue is purified by column chromatography eluting with 10% EtOAc/Hex to give 85% of **186b**. $[M+H]^+$ = 251.7.

Alternate substitution of pyridazinone **186b** can be achieved via this step using MeOH rather than dioxane as a solvent, wherein the methoxy occupies the 5 position on the pyridazinone ring and the chloro resides at the 4 position.

186C. Pyridazinone **186b** (1 mmol) is dissolved in DME. To this mixture is added $Pd(PPh_3)_4$ (10 mol%) and the mixture is stirred at room temperature for 10 min before 4 methoxybenzeneboronic acid (2 mmol) and aqueous 1 mL of Na_2CO_3 (10 wt%) are added. Subsequently, the reaction mixture is heated to reflux for 18 hours. The cooled reaction mixture is diluted with water and extracted 3 times with ethyl acetate. The combined organic layers are dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by column chromatography on silica gel eluting with 15% EtOAc/Hexane to give compound **186c**. $[M+H]^+ = 323.3$.

186D. To a solution of **186c** (3 mmol) in DME is added 2N KOH and the resulting mixture is heated to reflux for 1 hour. The cooled mixture is diluted with water and acidified with solid citric acid to pH ~ 5 and extracted 3 times with CH_2Cl_2. The organic layers are washed once with brine, dried ($MgSO_4$), filtered and concentrated under vacuum to give compound **186d**. $[M+H]^+ = 309.3$.

186E. To a cooled solution of compound **186d** (2 mmol), triethylamine (0.4 mL) in dichloromethane (10 mL) (ice-acetone bath) is added trifluoromethanesulfonic anhydride (0.4 mL) dropwise. The resulting solution is stirred for 30 min at –5°C. The reaction mixture is then poured into dilute HCl (0.5 M) and extracted with CH_2Cl_2. The combined organic layers are washed with a 1% $NaHCO_3$, brine and dried ($MgSO_4$), filtered and concentrated under vacuum to give a brown oil. Compound **186e** is used immediately without further purification. $[M+H]^+ = 441.4$.

186F. Commercially available 2,4-dibromothiazole (2 mmol) is dissolved in cyclopropylamine (3 mL) and the reaction mixture is heated to 50°C for 8 hour. The cooled mixture is then poured into water and extracted 2 times with ether. After drying the combined organic fractions ($MgSO_4$), evaporation of solvents, and purification by flash column chromatography (silica gel, 15% EtOAc/Hexane) furnished 2-cyclopropylamine-4-bromothiazole which is further converted to the corresponding stannane **186f**. A solution of 2-cyclopropylamine-4-bromothiazole in degassed DME is treated with hexamethylditin and $Pd(PPh_3)_4$ and heated at 80°C for 18 hour. The cooled

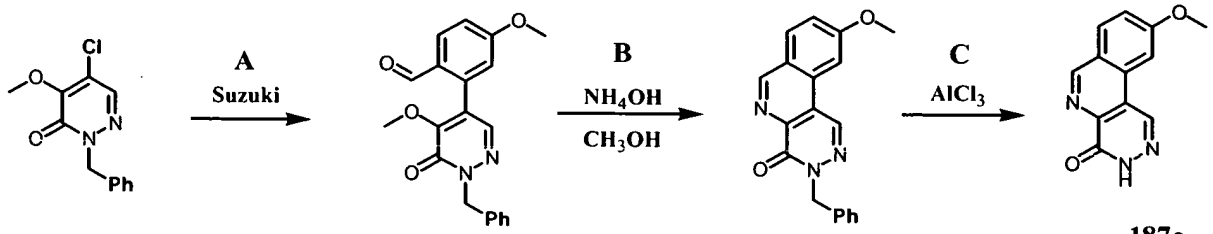
mixture is concentrated under vacuum and the residue is purified by column chromatography eluting with 20% EtOAc/Hexane/2%Et_3N to give Stannane **186f**. $[M+H]^+$ = 304.1.

186G. To a degassed solution of compound **186e** (1 mmol) and stannane **186f** (2 mmol) is added $Pd(PPh_3)_4$ (10 mol%). The mixture is degassed two additional times with nitrogen and subsequently heated to 100 °C for 3 hour. The cooled mixture is concentrated under vacuum and the residue is purified by column chromatography eluting with 30% EtOAc/Hexane to give compound **186g**. $[M+H]^+$ = 431.6.

186H. A solution of compound **186g** and 10% Pd/C (wet) in MeOH is subjected to a hydrogen balloon for 2 hours. The mixture is filtered through a pad of celite and the filtrate is concentrated under vacuum to give compound **186h**. $[M+H]^+$ = 341.4.

The title compound is prepared from pyridazinone **186h** and the cyclic peptide precursor **1** of Example 1 via the Mitsunobu conditions set forth in Example 158, followed by the hydrolysis of the ethyl ester via the hydrolysis conditions described in Example 159.

Example 187. Compound of Formula II, wherein A = tBOC, G = OH, L = absent, X and Y taken together = 6-methoxy-isoquinolin-(3,4)-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.



187A. Pyridazinone **186b** (2 mmol) is dissolved in DME. To this mixture is added $Pd(PPh_3)_4$ and the mixture is stirred at room temperature for 10 min before 2-

formyl-4- methoxybenzeneboronic acid and aqueous Na_2CO_3 (10 wt%) are added. Subsequently, the reaction mixture is heated to reflux for 18 hours. The cooled reaction mixture is diluted with water and extracted 3 times with ethyl acetate. The combined organic layers are dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by column chromatography on silica gel eluting with 20% EtOAc/Hexane to give compound **187a**. $[M+H]^+ = 351.4$.

187B. A mixture of pyridazinone **187a** (1 mmol), MeOH (20 mL) and NH_4OH (10 mL, 28-30 wt%) is heated at 60°C for 30 min. After cooling, the precipitate, compound **187b**, is filtered and rinsed with MeOH (15 mL). $[M+H]^+ = 317.4$.

187C. A mixture of pyridazinoisoquinolinone **187b** (0.5 mmol), $AlCl_3$ and toluene is stirred and heated at 70°C for 1 hour. After cooling, water is added and the mixture is filtered and rinsed with water. The residue is purified by column chromatography on silica gel eluting with 50% EtOAc/Hex to give compound **187c**. $[M+H]^+ = 227.3$.

The title compound is prepared from pyridazinoisoquinolinone **187c** and the cyclic peptide precursor **1** of Example 1 via the Mitsunobu conditions set forth in Example 162, followed by the hydrolysis of the ethyl ester via the hydrolysis conditions described in Example 159.

Example 188. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

188a– Amine deprotection.

0.041mmol of the title compound of Example 159 is dissolved in 4ml of a 4M solution of HCl in dioxane and stirred for 1 hour. The reaction residue **188a** is concentrated *in vacuo*.

188b – Chloroformate Reagent

The chloroformate reagent **188b** is prepared by dissolving 0.045mmol of cyclopentanol in THF (3ml) and adding 0.09mmol of phosgene in toluene (20%). The resulting reaction mixture is stirred at room temperature for 2 hours and the solvent is removed *in vacuo*. To the residue is added DCM and subsequently concentrated to dryness twice *in vacuo* yielding chloroformate reagent **188b**.

188c – Carbamate formation

The title carbamate is prepared by dissolving residue **188a** in 1ml of THF, adding 0.045mmol of TEA, and cooling the resulting reaction mixture to 0°C. To this 0°C reaction mixture is added chloroformate reagent **188b** in 3ml of THF. The resulting reaction mixture is reacted for 2 hours at 0°C, extracted with EtOAc, washed by 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 160.

Example 189. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclobutyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

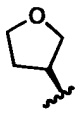
The title compound is prepared by the method described in Example 188 with the title compound of Example 159 and cyclobutanol.

Example 190. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 = cyclohexyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

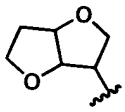
The title compound is prepared by the method described in Example 188 with the title compound of Example 159 and cyclohexanol.

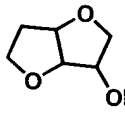
Example 191. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by the method described in Example 188 with the title compound of Example 159 and (R)-3-hydroxytetrahydrofuran.

Example 192. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by the method described in Example 188 with the title compound of Example 159 and (S)-3-hydroxytetrahydrofuran.

Example 193. Compound of Formula II, wherein A = –(C=O)–O–R^1, wherein R^1 =  , G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared by the method described in Example 188 with the title compound of Example 159 and  .

Example 194. Compound of Formula II, wherein A = –(C=O)–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound from Example 159 in 4ml of a 4M solution of HCl in dioxane and stirring the reaction mixture for 1 hour. The reaction residue is concentrated *in vacuo*. To this residue, 4ml of THF and 0.045mmol of TEA is added, the mixture is cooled to 0°C, to which is added 0.045mmol of the cyclopentyl acid chloride. The resulting reaction mixture is stirred for 2 hours at 0°C. The reaction mixture is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 160.

Example 195. Compound of Formula II, wherein A = –(C=O)–NH–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound from Example 159 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 160.

Example 196. Compound of Formula II, wherein A = –(C=S)–NH–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

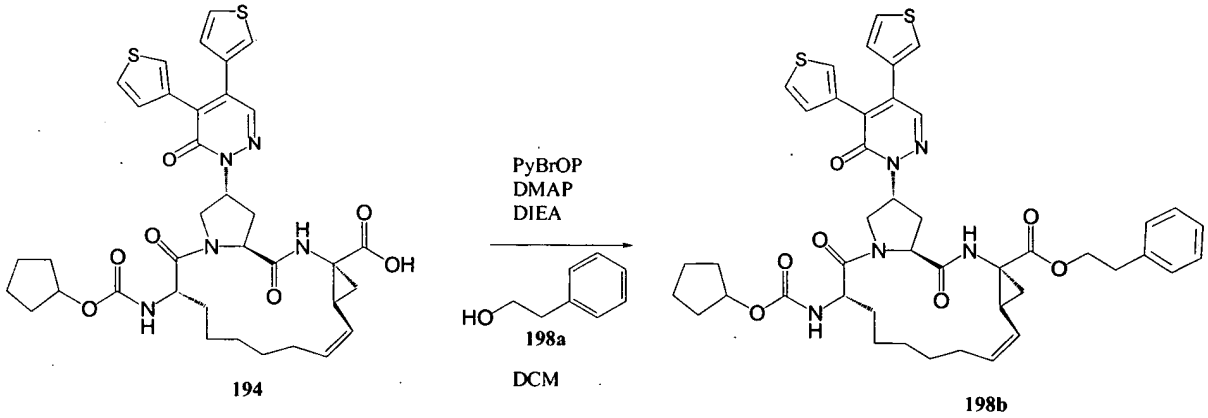
The title compound is prepared with the title compound from Example 159 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. The resulting reaction residue is concentrated *in vacuo*, dissolved in 4ml THF, and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl isothiocyanate and the resulting reaction mixture is stirred at RT for 4 hours. The solution is then extracted with EtOAc, washed with 1% HCl, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 160.

Example 197. Compound of Formula II, wherein A = –$S(O)_2$–R^1, wherein R^1 = cyclopentyl, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound from Example 159 in 4ml of a 4M solution of HCl in dioxane and stirring for 1 hour. To the resulting concentrated reaction residue, which has been dissolved in 4ml THF, is added 0.045mmol of TEA,

and cooled to 0°C. To the 0°C solution is added 0.045mmol of cyclopentyl sulfonyl chloride and the resulting reaction mixture is stirred at 0°C for 2 hours. The solution is then extracted with EtOAc, washed with 1M sodium bicarbonate, water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to dryness. The crude compound is purified by silica column and the ethyl ester is subsequently hydrolyzed by the procedure set forth in Example 160.

Example 198. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –O–phenethyl, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

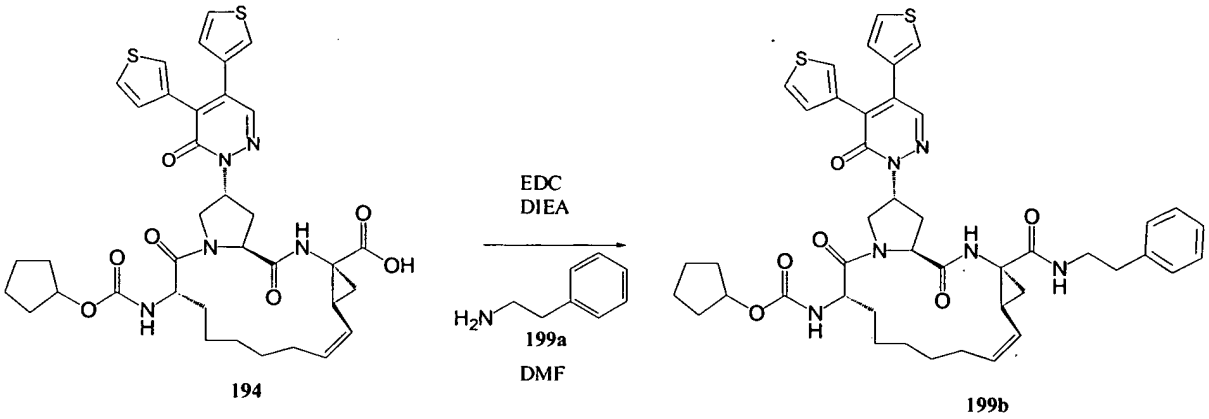


194 198b

The title compound is prepared by adding to a solution of the title compound of Example 194 and phenethyl alcohol **198a** in 0.5 ml DCM, is added 1.2 eq. PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at 0°C. The resulting reaction mixture is stirred for 1 hour at 0°C and then warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated phenethyl ester **198b**.

Other esters can be made using the same procedures.

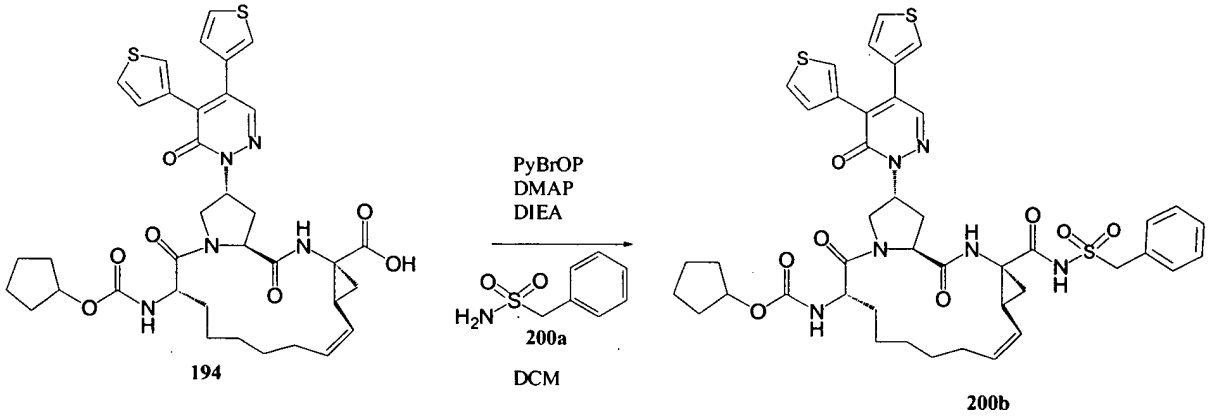
Example 199. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –NH–phenethyl, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.



The title compound is prepared by adding to a solution of the title compound of Example 194 and phenethylamine **199a** (0.05 ml) in 0.5 ml DMF, EDC (1.2 eq.) and DIEA (4eq.) at 0°C. The resulting reaction mixture is stirred at 1 hour. Subsequently, the reaction is warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford title compound phenethyl amide **199b**.

Other amides can be made via the same procedure.

Example 200. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –NHS(O)$_2$–phenethyl, L = absent X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

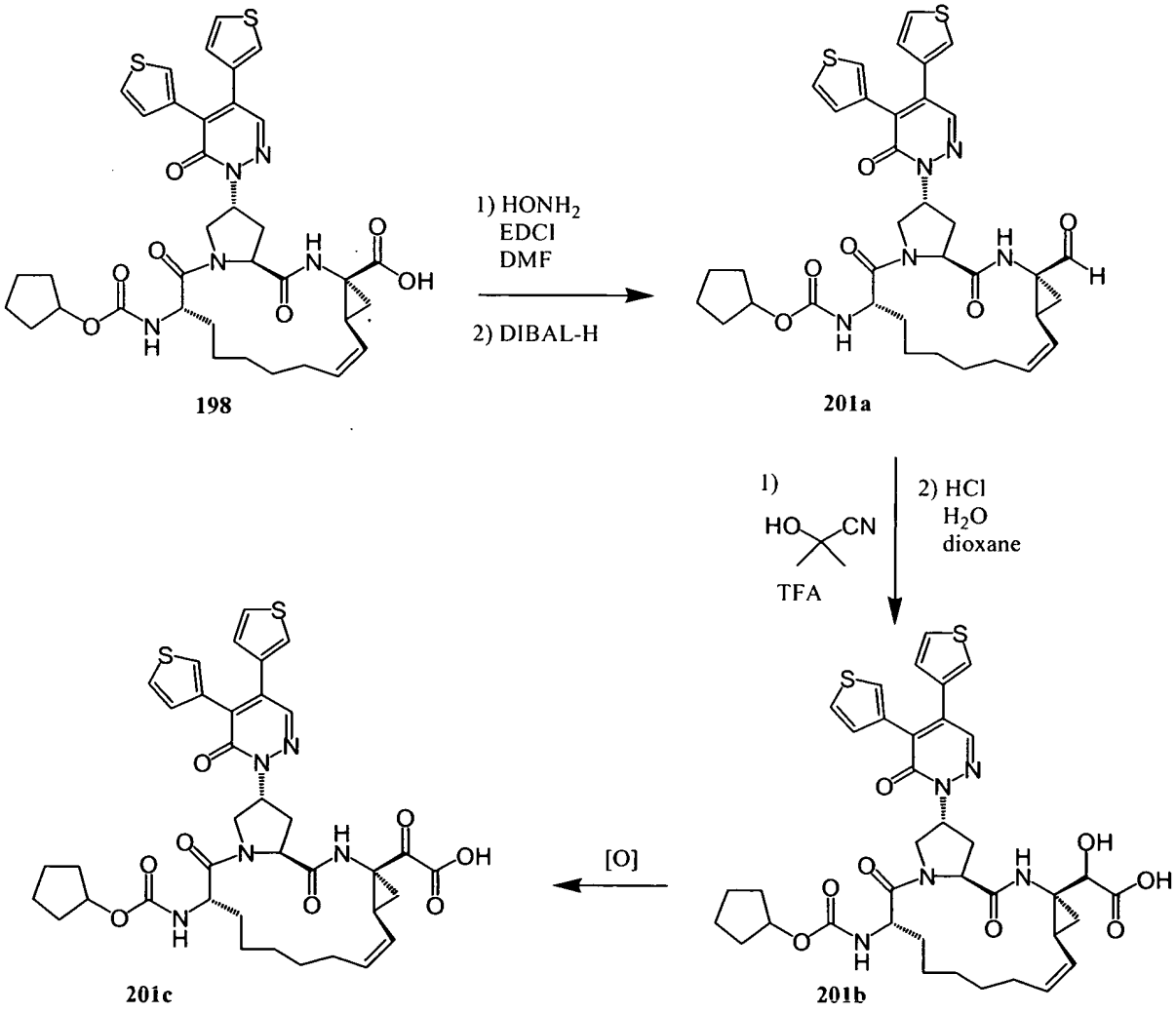


The title compound is prepared by adding to a solution of the title compound of Example 194 and α-toluenesulfonamide **200a** (10mg) in 0.5 ml DCM, is added 1.2 eq. PyBrOP, 4eq. DIEA, and catalytic amount of DMAP at 0°C. The resulting reaction mixture is stirred for 1 hour and then allowed to warm to RT over a period of 4-12 hours.

The reaction mixture is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound sulfonamide **200b**.

Other sulfonamides can be made via the same procedure.

Example 201. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and and R^3 = R^4 = hydrogen.



The title compound is prepared by adding to a solution of the title compound of Example 194 in 0.5 ml DMF, EDC (1.2 eq.) and DIEA (4eq.) at 0°C. The resulting reaction mixture is stirred at 1 hour. Subsequently, the reaction is warmed to RT over a period of 4-12 hours. The reaction mixture is purified by silica gel flash chromatography

to afford hydroxyamide. The hydroyamide is then treated with DIBAL-H at –78°C in THF for 2 hours. The reaction mixture is then diluted with 8 ml EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield aldehyde **201a.** To a solution of aldehyde **39a** in 0.5 ml THF, is added α-hydroxy-α-methyl-propionitrile (0.1 ml) and catalytic amount TFA at 0°C. The resulting reaction mixture is warmed from 0° C to RT over a period of 4-12 hours followed by hydrolysis with concentrated hydrochloric acid in dioxane. The reaction is then extracted with EtOAc, and washed with water and brine to yield α-hydroxy compound **201b** in its crude form. The crude compound **201b** undergoes a Dess-Martin oxidation in THF (0.5 ml), providing the α-carbonyl compound **201c** in crude form. The crude **201c** is purified by silica gel flash chromatography using different ratios of hexanes:EtOAc as elution phase (9:1→5:1→3:1→1:1) to afford the title compound isolated keto acid **201c**.

Example 202. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–O–phenethyl, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound keto acid of Example 201 and phenethanol according to the procedure set forth Example 198.

Example 203. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–NH–phenethyl, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound keto acid of Example 201 and phenethyl amine according to the procedure set forth in Example 199.

Example 204. Compound of Formula II, wherein A = –(C=O)–O–R^1, R^1 = cyclopentyl, G = –(C=O)–NH–$S(O)_2$–benzyl, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and R^3 = R^4 = hydrogen.

The title compound is prepared with the title compound keto acid of Example 201 and α-toluenesulfonamide according to the procedure set forth in Example 200.

Example 205. Compound of Formula II, wherein A = tBOC, G = OH, L = $-(C=O)CH_2-$, X = Y = thiophen-3-yl, Z = hydrogen, j = 1, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **88C** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

Example 206. Compound of Formula II, wherein A = tBOC, G = OH, L = $-CH(CH_3)CH_2-$, X = Y = thiophen-3-yl, Z = hydrogen, j = 1, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **89G** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

Example 207. Compound of Formula II, wherein A = tBOC, G = OH, L = –O–, X = Y = thiophen-3-yl, Z = hydrogen, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **90D** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

Example 208. Compound of Formula II, wherein A = tBOC, G = OH, L = –S–, X = Y = thiophen-3-yl, Z = hydrogen, j = 0, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **91E** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

Example 209. Compound of Formula II, wherein A = tBOC, G = OH, L = –S(O)–, X = Y = thiophen-3-yl, Z = hydrogen, j = 2, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **92B** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160.*

Example 210. Compound of Formula II, wherein A = tBOC, G = OH, L = $–S(O)_2$ X = Y = thiophen-3-yl, Z = hydrogen, j = 2, m = s = 1, R^3 = methyl, and R^4 = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **93B** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160.*

Example 211. Compound of Formula II, wherein A = tBOC, G = OH, L = $–SCH_2CH_2–$, X = Y = thiophen-3-yl, Z = hydrogen, j = 0, m = s = 1, and $R^3 = R^4 = CH_3$.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **94B** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160.*

Example 212. Compound of Formula II, wherein A = tBOC, G = OH, L = CF_2CH_2, X = Y = thiophen-3-yl, Z = hydrogen, j = 1, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **95C** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160.*

Example 213. Compound of Formula II, wherein A = tBOC, G = OH, L = $-CHFCH_2-$, X = Y = thiophen-3-yl, Z = hydrogen, j = 1, m = s = 1, and $R^3 = R^4$ = hydrogen.

The title compound is prepared with the modified cyclic peptide precursor mesylate formed in **96C** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

Example 214. Compound of Formula III, wherein A = tBOC, G = OH, L = absent, X = Y = thiophen-3-yl, Z = hydrogen, j = 3, m = s = 1, and $R^3 = R^4$ = hydrogen.

214A. The saturated cyclic peptide precursor mesylate is prepared by catalytic reduction of the mesylate cyclic peptide precursor of Example 2 with Pd/C in MeOH in the presence of H_2.

The title compound is prepared with the saturated cyclic peptide precursor mesylate formed in **214A** and 4,5-di(thiophen-3-yl)-2H-pyridazin-3-one by the Mitsunobu conditions elucidated in Example 158 followed by hydrolysis of the ethyl ester via the method set forth in *Example 160*.

The compounds of the present invention exhibit potent inhibitory properties against the HCV NS3 protease. The following examples elucidate exemplary assays in which the compounds of the present invention are tested for anti-HCV effects.

Example 215. NS3/NS4a Protease Enzyme Assay

HCV protease activity and inhibition is assayed using an internally quenched fluorogenic substrate. A DABCYL and an EDANS group are attached to opposite ends of a short peptide. Quenching of the EDANS fluorescence by the DABCYL group is relieved upon proteolytic cleavage. Fluorescence was measured with a Molecular Devices Fluoromax (or equivalent) using an excitation wavelength of 355 nm and an emission wavelength of 485 nm.

The assay is run in Corning white half-area 96-well plates (VWR 29444-312 [Corning 3693]) with full-length NS3 HCV protease 1b tethered with NS4A cofactor (final enzyme concentration 1 to 15 nM). The assay buffer is complemented with 10 μM NS4A cofactor Pep 4A (Anaspec 25336 or in-house, MW 1424.8). RET S1 (Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-[COO]Ala-Ser-Lys-(DABCYL)-NH_2, AnaSpec 22991, MW 1548.6) is used as the fluorogenic peptide substrate. The assay buffer contained 50 mM Hepes at pH 7.5, 30 mM NaCl and 10 mM BME. The enzyme reaction is followed over a 30 minutes time course at room temperature in the absence and presence of inhibitors.

The peptide inhibitors HCV Inh 1 (Anaspec 25345, MW 796.8) Ac-Asp-Glu-Met-Glu-Glu-Cys-OH, [-20^{0}C] and HCV Inh 2 (Anaspec 25346, MW 913.1) Ac-Asp-Glu-Dif-Cha-Cys-OH, were used as reference compounds.

IC50 values were calculated using XLFit in ActivityBase (IDBS) using equation 205: y=A+((B-A)/(1+((C/x)^D))).

Example 216. Cell-Based Replicon Assay

Quantification of HCV replicon RNA in cell lines (HCV Cell Based Assay)

Cell lines, including Huh-11-7 or Huh 9-13, harboring HCV replicons (Lohmann, et al Science 285:110-113, 1999) are seeded at 5x10^3 cells/well in 96 well plates and fed media containing DMEM (high glucose), 10% fetal calf serum, penicillin-streptomycin and non-essential amino acids. Cells are incubated in a 5% CO_2 incubator at 37 °C. At the end of the incubation period, total RNA is extracted and purified from cells using Qiagen Rneasy 96 Kit (Catalog No. 74182). To amplify the HCV RNA so that sufficient material can be detected by an HCV specific probe (below), primers specific for HCV (below) mediate both the reverse transcription of the HCV RNA and the amplification of the cDNA by polymerase chain reaction (PCR) using the TaqMan One-Step RT-PCR Master Mix Kit (Applied Biosystems catalog no. 4309169). The nucleotide sequences of the RT-PCR primers, which are located in the NS5B region of the HCV genome, are the following:

HCV Forward primer "RBNS5bfor"

5'GCTGCGGCCTGTCGAGCT:

HCV Reverse primer "RBNS5Brev":

5'CAAGGTCGTCTCCGCATAC

Detection of the RT-PCR product was accomplished using the Applied Biosystems (ABI) Prism 7700 Sequence Detection System (SDS) that detects the fluorescence that is emitted when the probe, which is labeled with a fluorescence reporter dye and a quencher dye, is processed during the PCR reaction. The increase in the amount of fluorescence is measured during each cycle of PCR and reflects the increasing amount of RT-PCR product. Specifically, quantification is based on the threshold cycle, where the amplification plot crosses a defined fluorescence threshold. Comparison of the threshold cycles of the sample with a known standard provides a highly sensitive measure of relative template concentration in different samples (ABI User Bulletin #2 December 11, 1997). The data is analyzed using the ABI SDS program version 1.7. The relative template concentration can be converted to RNA copy numbers by employing a standard curve of HCV RNA standards with known copy number (ABI User Bulletin #2 December 11, 1997).

The RT-PCR product was detected using the following labeled probe:

5' FAM-CGAAGCTCCAGGACTGCACGATGCT-TAMRA

FAM= Fluorescence reporter dye.

TAMRA:=Quencher dye.

The RT reaction is performed at 48 °C for 30 minutes followed by PCR. Thermal cycler parameters used for the PCR reaction on the ABI Prism 7700 Sequence Detection System were: one cycle at 95 °C, 10 minutes followed by 35 cycles each of which included one incubation at 95 °C for 15 seconds and a second incubation for 60 °C for 1 minute.

To normalize the data to an internal control molecule within the cellular RNA, RT-PCR is performed on the cellular messenger RNA glyceraldehydes-3-phosphate

dehydrogenase (GAPDH). The GAPDH copy number is very stable in the cell lines used. GAPDH RT-PCR is performed on the same exact RNA sample from which the HCV copy number is determined. The GAPDH primers and probes, as well as the standards with which to determine copy number, are contained in the ABI Pre-Developed TaqMan Assay Kit (catalog no. 4310884E). The ratio of HCV/GAPDH RNA is used to calculate the activity of compounds evaluated for inhibition of HCV RNA replication.

Activity of compounds as inhibitors of HCV replication (Cell based Assay) in replicon containing Huh-7 cell lines

The effect of a specific anti-viral compound on HCV replicon RNA levels in Huh-11-7 or 9-13 cells was determined by comparing the amount of HCV RNA normalized to GAPDH (e.g. the ratio of HCV/GAPDH) in the cells exposed to compound versus cells exposed to the 0% inhibition and the100% inhibition controls. Specifically, cells were seeded at 5x 10^3 cells/well in a 96 well plate and were incubated either with: 1) media containing 1% DMSO (0% inhibition control), 2) 100 international units, IU/ml Interferon-alpha 2b in media/1%DMSO or 3) media/1%DMSO containing a fixed concentration of compound. 96 well plates as described above were then incubated at 37 °C for 3 days (primary screening assay) or 4 days (IC50 determination). Percent inhibition was defined as:

% Inhibition= [100-((S-C2)/C1-C2))]x100

where

S= the ratio of HCV RNA copy number/GAPDH RNA copy number in the sample;

C1= the ratio of HCV RNA copy number/GAPDH RNA copy number in the 0% inhibition control (media/1%DMSO); and

C2= the ratio of HCV RNA copy number/GAPDH RNA copy number in the 100% inhibition control (100 IU/ml Interferon-alpha 2b).

The dose-response curve of the inhibitor was generated by adding compound in serial, three-fold dilutions over three logs to wells starting with the highest concentration

of a specific compound at 10uM and ending with the lowest concentration of 0.01uM. Further dilution series (1uM to 0.001uM for example) was performed if the IC50 value was not in the linear range of the curve. IC50 was determined based on the IDBS Activity Base program using Microsoft Excel "XL Fit" in which A=100% inhibition value (100IU/ml Interferon-alpha 2b), B= 0% inhibition control value (media/1%DMSO) and C= midpoint of the curve as defined as C=(B-A/2)+A. A, B and C values are expressed as the ratio of HCV RNA/GAPDH RNA as determined for each sample in each well of a 96 well plate as described above. For each plate the average of 4 wells were used to define the 100% and 0% inhibition values.

Although the invention has been described with respect to various preferred embodiments, it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.